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CONTENTS AND SUBJECT INDEX

Clinical Research in Private Practice. Wingate M. Johnson, M.D., Winston-Salem, N. C.....215

Sites of Metastases from Carcinoma of the Anus, Rectum and Sigmoid Colon. Harry E. Bacon, M.D., and Philip D. Gilbert, M.D., Philadelphia 219

Thrombocytopen: A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces the Number of Blood Platelets. C. E. Troland, M.D., and F. C. Lee, M.D., Baltimore.....221

The Use of Sulfanilamide in the Diagnosis and Treatment of Brucellosis. Henry Welch, Ph.D.; John A. Wentworth, M.D., and Friend Lee Mickle, Sc.D., Hartford, Conn.....226

The Lateral Pyelogram as a Diagnostic Aid in Perinephric Abscess. John G. Menville, M.D., New Orleans 231

Fibrous and Fatty Replacement of Renal Parenchyma. Louis J. Roth, M.D., and Horace B. Davidson, M.D., Columbus, Ohio.....233

CLINICAL NOTES, SUGGESTIONS AND NEW INSTRUMENTS

Osteoma of Frontal Sinus and Penetration of Lateral Ventricle, with Intermittent Pneumocephalus. Eldridge H. Campbell, M.D., and R. B. Gottschalk, A.B., Albany, N. Y.....239

Fracture of the Optic Canal Causing Optic Atrophy. Eugene Freedman, M.D., Cleveland.....241

Hereditary Multiple Telangiectasis with Epistaxis: Method of Treatment. George Hunter O'Kane, M.D., New York.....242

SPECIAL ARTICLE

Vitamin A: Methods of Assay and Sources in Food. Hazel E. Munsell, Ph.D., Washington, D. C...245

COUNCIL ON PHYSICAL THERAPY 252

COUNCIL ON PHARMACY AND CHEMISTRY 253

COUNCIL ON FOODS 253

EDITORIALS

Danger of Protamine Insulins....254

Standardization of Liver Preparations 254

Examinations for Domestics.....255

Renal Rickets.....256

CURRENT COMMENT

What Is Adequate Hospital Service? 257

Maternal Age and Mongolism....257

Deficiency of Vitamin B and Pediculosis 257

Map Showing Distribution of Hospitals in the United States....258

BUREAU OF LEGAL MEDICINE AND LEGISLATION 279

(Subject Index on next page)

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Other SAUNDERS BOOKS Described on Pages 3, 4, 5

SUBJECT INDEX TO THIS ISSUE

The letters used to explain in which department the matter indexed appears are as follows: The Star (*) indicates an Original Article; "ab," abstract; "E," Editorial; "C," Correspondence; "Ml," Medicolegal; "ME," Medical Economics; "OS," Organization Section.

Abortion: accidental; shock in relation to..Ml-280
wheat germ oil (vitamin E) in.....ab-285
Abscess, perinephric, lateral pyelogram as diagnostic aid in.....*231
Accidents from fireworks, broadcast on.....262
Acid, ascorbic, in fetal blood.....ab-284
ascorbic, response to.....ab-283
tannic, nasal sprays and catarrh.....ab-284
Age, maternal, and mongolism.....E-257
Alcohol absorption through skin.....271
"normal," in tissues.....271
Allergic blepharitis 274
Alvarenga Prize awarded to Dr. Richard Edwin Shope 261
Anus, carcinoma of, sites of metastases from *219
Arnica flowers, poisoning with tea from..ab-290
Arthus phenomenon from mosquito bites..ab-285
Asthmatic attacks from coal gas.....272

Bliss (Malcolm A.) Psychopathic Institute, cornerstone laid for.....261
Blood chemistry and metrazol convulsions.ab-281
circulation, German society for study of..266
platelets, thrombocytopen reduces number of *221
transfusion, plan to organize society for..262
Board Examinations.....275
Bone and cartilage in scurvy.....ab-281
Book Notices.....276
Books Received.....**Adv. page 30**
Brain, encephalographic aspects of epilepsy ab-288
Bureau of Legal Medicine and Legislation...279

Cancer, sites of metastases from carcinoma of the anus, rectum and sigmoid colon..*219
Women's Field Army, assembly of.....262
Carbon Monoxide poisoning, chronic, or neurosis 272
Cartilage and bone in scurvy.....ab-281
Catarrh, tannic acid nasal sprays and....ab-284
Cerebrospinal Fluid, tumor cells in.....ab-287
Cholera epidemics 263
Coal gas, asthmatic attacks from.....272
Cocaine hydrochloride solutions, sterilization of 272
Congress on Renal Insufficiency.....263
on Rheumatism in New York, 1940.....263
Correspondence 269
Council on Foods.....253
Council on Pharmacy and Chemistry.....253
Council on Physical Therapy.....252
Crippled children, commission to study, New York City 262

Deaths 268
Dextrose, influence on inoculation malaria..ab-289
Diuresis, mercurial suppositories and.....ab-282
Domestics, medical examinations for.....E-255
Dusts, excretion from lungs.....ab-282
Dwarfism, renal rickets E-256

Electrosterilization of root canals.....274
Encephalitis, acute, after infections.....ab-289
Epilepsy, encephalographic aspects.....ab-288
Ethyl amyl ketone, possible toxic effect from metal cleaner 272
Eyelids, allergic blepharitis.....274

Fetus, ascorbic acid in fetal blood.....ab-284
Fever treatment of neurologic conditions....266
Fireworks, accidents from, broadcast on.....262
Fluorine poisoning 273
Foreign Letters.....264

Goiter, lymphadenoid ab-283
Golf tournament in San Francisco, report...263
Gonorrhea, in children, sulfanilamide in..ab-285
in the female 265

Harrington, Francis E., honored.....261
Health insurance, national, difficulties.....267
Heart, respiratory variations of cardiac systole ab-287
Hines, Edgar A., honored.....262
Hormone pregnancy reactions.....ab-288
Hospital service, what is adequate?.....E-257
map showing distribution in U. S.....E-258
Hypothalamus, histologic examination of, in obesity ab-289

Industrial cutaneous diseases.....266
hazards, survey, Indiana.....260
Infants, Newborn, prevention of cutaneous infection of ab-284
Infections, acute encephalitis after.....ab-289
focal infections ab-290
pneumococcic, chemotherapy of.....264
Insulins, protamine, danger of.....E-254
Insurance, health, national, difficulties.....267
national, Sir Walter Kinnear called to America 267
social, and private practice.....264
Intestines, sites of metastases from carcinoma of sigmoid colon.....*219

Kidneys, fibrous and fatty replacement of renal parenchyma *233
renal rickets E-256
Kinnear, Sir Walter, called to America....267

Leukocytosis in lymphoblastoma.....ab-282
Leukopenia and leukocytosis in lymphoblastoma ab-282
Lipoma and lipuria.....273
Lipuria, lipoma and.....273
Liver, fatty infiltration of, and cirrhosis.ab-281
preparations, standardization of.....E-254
sciatic neuritis and hepatic disease.....ab-283
Lungs, excretion of dusts from.....ab-282
Lymphoblastoma, leukopenia and leukocytosis in ab-282

Malaria, inoculation, influence of dextrose on ab-289
Malariology course in Rome.....263
Marriages 267
Maternal age and mongolism.....E-257
Measles, prevention ab-286
Medical Examinations and Licensure.....275
Medical examinations for domestics.....E-255
Medical Practice, private, clinical research in *215
private, and social insurance.....264
Medicolegal Abstracts.....279
Meetings, Coming Meetings.....280
Meningitis, control C-269
Mental disease, blood chemistry and metrazol convulsions ab-281
disorder, nasal sinusitis and.....ab-286
Mercurial suppositories and diuresis.....ab-282
Metal cleaner, possible toxic effect from.....272
Metrazol convulsions, blood chemistry and.ab-281
Meyerding, Edward A., resigns—receives award 261
Mongolism, maternal age and.....E-257
Mosquito bites, Arthus phenomenon from..ab-285

Nail biting and thumb sucking.....273
Nerve, optic, fracture of optic canal causing optic atrophy *241
Neuritis, sciatic, and hepatic disease....ab-283
Neurology, fever treatment of neurologic conditions 266
Neurosis, chronic carbon monoxide or.....272
Neurotonic reactions, reflexotherapy of...ab-287
New and Nonofficial Remedies.....253
News 260
Nose, hemorrhage, hereditary multiple telangiectasis with, treatment.....*242
nasal sinusitis and mental disorder.....ab-286
tannic acid nasal sprays and catarrh....ab-284

Obesity, histologic examination of hypothalamus in ab-289
Obstetrics, graduate course in, Chicago.....260
Ohio State University has received gift for research 262
Optic canal, fracture of, causing optic atrophy *241
Optometry Practice Acts: licenses; revocation; notice to licentiate required....Ml-279
Osteoma of frontal sinus and penetration of lateral ventricle, with intermittent pneumocephalus *239

Parenchyma, renal, fibrous and fatty replacement of *233
Pediatrics, German Society of, meeting.....265
graduate course in, Chicago.....260
Pediculosis, vitamin B deficiency and....E-257
Penis, diagnosis of penile ulcers.....274
Perinephric abscess, lateral pyelogram as diagnostic aid in.....*231
Physical exertion and poliomyelitis.....ab-289
Plague infection in Santa Cruz County.....260
Pneumocephalus, intermittent, osteoma of frontal sinus and penetration of lateral ventricle, with *239
Pneumococcic infections, chemotherapy of...264
Poisoning from tea with arnica flowers...ab-290
Poliomyelitis, physical exertion and.....ab-289
Pregnancy, hormone pregnancy reactions.ab-288
effects of operations on cervix on.....264
Privileged Communications: waiver; testimony of patient.....Ml-279
Prize, Alvarenga, awarded to Dr. Richard Edwin Shope 261
Prostate, breaking of prostatic ring.....ab-290
Protamine insulins, danger of.....E-254
Psychopathic Institute, Malcolm A. Bliss, cornerstone laid for.....261
Purpura, thrombocytopenic, thrombocytopen, substance in extract from spleen of patients with *221
Pyelogram, lateral, as diagnostic aid in perinephric abscess *231

Queries and Minor Notes.....271

Rectum, carcinoma of, sites of metastases from *219
Reflexotherapy of neurotonic reactions....ab-287
Renal Insufficiency, Congress on.....263
Rendu-Osler-Weber disease, hereditary multiple telangiectasis with epistaxis; treatment *242
Research, clinical, in private medical practice *215
gift for, at Ohio State University.....262
Respiration, respiratory variations of cardiac systole ab-287
Rheumatism, Congress on, in New York, 1940 263
Rickets, renal E-256
Rural hygiene, conference on, Mexico City..263

Scurvy, bone and cartilage in.....ab-281
Serums, effect of storing, on Wassermann reaction 275
Shellfish from Bay area banned, New Hampshire 261
Shope, Richard Edwin, awarded Alvarenga Prize 261
Sinus, frontal, osteoma of, and penetration of lateral ventricle, with intermittent pneumocephalus *239
Sinusitis, nasal, and mental disorder.....ab-286
Skin, prevention of cutaneous infection of newborn ab-284
diseases, industrial 266
Society Proceedings.....280
Spleen, thrombocytopen: substance in extract from spleen of patients with idiopathic thrombocytopenic purpura *221
State Board Examinations.....275
Sterilization of cocaine hydrochloride solutions 272
Sulfanilamide in gonococcic infections in children ab-284
in trachoma ab-290
use in diagnosis and treatment of brucellosis *226
Syphilis, rate in domestics.....E-255

Tea from arnica flowers, poisoning from..ab-290
Teeth, electrosterilization of root canals.....274
Thrombocytopen *221
Thumb sucking and nail biting.....273
Tonics and Sedatives.....**Adv. page 24**
Trachoma, sulfanilamide in.....ab-290
Tuberculins, investigations on.....ab-286
Tuberculosis, vaccination for.....ab-288
seminar on, North Carolina.....262
Tumor cells in cerebrospinal fluid.....ab-287

Ulcers, penile, diagnosis.....274
Undertakers, registration of.....264
Undulant Fever, brucellosis in and around Vancouver ab-283
sulfanilamide in diagnosis and treatment.*226
Urticaria pigmentosa 273
Uterus, effects on pregnancy of operations on cervix 264

Vaccination for tuberculosis.....ab-288
Vitamin A; methods of assay and sources in food *245
B deficiency and pediculosis E-257
C, response to ascorbic acid.....ab-283
E, wheat germ oil in abortion.....ab-285

Warnshuis, Frederick C., goes to Massachusetts 260
Wassermann reaction, effect of storing serums on 275
Wheat germ oil (vitamin E) in abortion..ab-285
Women's Field Army of American Society for the Control of Cancer, assembly of..262
Workmen's Compensation Acts: heat stroke Ml-280
ureters; kinking attributed to strain..Ml-280

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CLINICAL RESEARCH IN PRIVATE PRACTICE

WINGATE M. JOHNSON, M.D.

WINSTON-SALEM, N. C.

"Let your light so shine before men, that they may see your good works" (Matthew 5:16).

A recent book by Stuart Chase has a most fascinating title—"The Tyranny of Words." The very name is enough to stimulate endless reflection as to how almost everybody, no matter how intelligent, is influenced, if not dominated, by the meaning attached to certain words or phrases. How contradictory may be one's reactions to different terms with virtually the same meanings! For example, it makes all the difference whether a woman is called "slender" or "skinny," "fat" or "pleasingly plump"; whether a man is called "generous" or "spendthrift," "thrifty" or "stingy," "conservative" or "a mossback reactionary," "liberal" or "radical"; whether he is said to have "the courage of his convictions" or to be "as stubborn as a mule." A college student appreciates being told he has the power of concentration but resents being called a "dig" or "grind." No doubt the central character in the Bible's best known parable was often flattered, so long as his money lasted, by the ancient equivalent of "He's a jolly good fellow" before he was immortalized as the Prodigal Son.

To most doctors, doubtless the first and most important meaning of the word "research" is work done in a great laboratory with thousands of dollars' worth of apparatus. The second idea suggested is a large hospital, with hundreds of patients separated into two great groups labeled "test" and "control." Perhaps a third conception is some such project as was recently completed by the United States Public Health Service, aided by one of the alphabetical arrangements of the federal government, in which a survey of nearly 800,000 families in the nation was made in order to find out what any intelligent high school student could have predicted—that there was more sickness in the families on relief and with annual incomes of less than $1,000 than in the upper income group. Apparently the conclusion was reached—which the same high school student would know is erroneous—that the only remedy needed is to have as many doctors' visits made to the low income group as to these in the higher brackets. While this conclusion is extremely flattering to our profession, none know better than we how sadly this low-income group needs sufficient food and warm clothing and adequate houses and fuel even more than it needs doctors' visits.

The average family doctor is likely to be so overawed by the majesty of the word "research" that he refuses to entertain for a moment the thought that he himself is capable of doing it while engaged in active practice. In truth, however, he is in a better position to do clinical research because he is in practice. Instead of working with rats, rabbits and guinea pigs, he has at hand the finest material in the world to use for study—the human beings who come to him for treatment. One can carry on one bit of investigation after another, or work on a number of problems together, and do better work for having a stimulating new interest added to the daily routine of practice. An utterly false conception of research is that it makes a man cold, heartless and indifferent to human suffering.

Before we tamely submit to the tyranny of the fearsome word "research," let us see just what it does mean. According to the Standard Dictionary, Webster concurring, it means "diligent protracted investigation, especially for the purpose of adding to human knowledge; studious inquiry." "Clinical," of course, is derived from the Greek word "klinikos," meaning "of a bed," with a second less aristocratic choice of ancestry in the Low Latin "clinicus," meaning "bedridden person." Our title, then, means "a studious inquiry of bedridden (or sick) people." Certainly every general practitioner worth his salt does just that every day of the week, including Sunday. It is the first part of the definition that may be forbidding at first glance; but closer inspection should make us feel more kindly toward it. Surely every doctor with a puzzling professional problem in the form of a serious, long drawn out illness will make "diligent protracted investigation" into the cause and (if possible) cure of his patient. When he has found the answer, if his experience will help other doctors solve similar problems, of course he will want to share his knowledge with his colleagues by telling them about it, thereby "adding to human knowledge" and engaging in "research" unawares. If, instead of a single patient studied intensively, a series of similar cases offers an opportunity to compare different methods of treatment or to evaluate a new remedy, a statistical study forms the basis for research of a different sort, but also valuable. Then, if the doctor extends his audience from a few friends to the county, district or state society or a medical journal—or both—he is indeed "adding to human knowledge." Any one who has ever done any bit of investigation knows that he himself profits more than anybody else. It is almost, if not quite, an invariable rule that he who tries to teach others will learn far more than he will teach.

Presidential address, read before the North Carolina State Medical Society, Pinehurst, April 3, 1938.

THE ABILITY OF FINDING VALUABLE THINGS UNEXPECTEDLY

I wish that every doctor in North Carolina could have heard Dr. Milton J. Rosenau's address to the State Public Health Association last year on "Serendipity." Let me hasten to explain that Serendip was the name that Marco Polo gave Ceylon and that Dr. Rosenau got his title from a fairy story of three princes of Serendip who "went about the world seeking adventures and making discoveries, by accident and sagacity, of things they were not in search of."

The doctor who carries into the practice of medicine something of serendipity will be repaid many times over; but he should also remember and absorb the famous saying of Pasteur "Chance favors the prepared mind" and have his mental antennae tuned to catch any important message that may come his way. It was the prepared mind and the spirit of serendipity that enabled Ambroise Paré to forsake the brutal method of dressing gunshot wounds with boiling oil; that made William Withering learn from an old woman the value of digitalis; that impelled John Hunter to do his pioneer work in surgical pathology and to elevate surgery from a trade to a profession; that gave to us through Jenner vaccination against smallpox; that caused William Beaumont to turn a French-Canadian's gunshot wound into an opportunity to study the physiology of gastric digestion; that led Crawford W. Long to use ether for anesthesia; that made Oliver W. Holmes and Semmelweis grasp the true explanation for childbed fever; that inspired Pasteur in his many brilliant discoveries; that gave Koch his triumphant discovery of the tubercle bacillus; that opened Roentgen's eyes to the wonderful possibilities in a Crookes tube. Coming to more modern times, the prepared mind of George Minot found a cure for pernicious anemia; Banting's isolated insulin; von Jauregg's recognized the value of malarial paroxysms in dementia paralytica; our own William MacNider's has made him an international authority on the kidney; our own David Smith's has taught us to treat pellagra and staphylococcic septicemia.

The family doctor in the small town or rural district has at least one distinct advantage over the hospital worker: his practice is a much more stable one, and it is easier to follow up his cases and so evaluate the results of treatment. His patients are also apt to be more intelligent and so more cooperative than are those who come to the wards and dispensaries of a great hospital. Those who have heard Dr. Walter C. Alvarez talk must have been impressed by the emphasis he places on the use of one's five natural senses, plus the priceless ingredient of common sense. Moreover, while the country doctor may not have the elaborate facilities of a great laboratory, he should have a few test tubes, a Bunsen burner or alcohol lamp, a microscope, a blood counting apparatus, glass slides, a few stains and the chemical reagents required to make the simple tests often needed to confirm a clinical diagnosis. Wassermann tubes are to be had for the asking, and the state laboratory sends reports promptly not only on Wassermann tests but also on typhoid, undulant fever and other serologic examinations.

With such aids to an adequately taken history and a complete physical examination, the family doctor should be able to diagnose and treat most of his patients himself and to know when the help of a surgeon or specialist is needed. Then if he will train himself from the beginning to keep records of his patients, he will be laying the foundation for one piece of research after another. The habit of keeping in mind for study some problem, or even several problems, adds immeasurably to the zest of practice. It gives the spice of adventure to what may otherwise become deadening routine. Furthermore, the answer to a hard professional riddle may be found because one has the riddle in mind. Only too many of us are like the Negro who, when something was explained in terms he could understand, exclaimed "Why, I never thought to think about that." Recently a brilliant research worker in physics said that when any important discovery in physics is announced it is at once tried out in his laboratory. Almost invariably he finds it easily duplicated with his apparatus. All that was necessary was the thought to think about it. The same thing could be said of many, if not most, great medical discoveries.

ESSENTIALS FOR CLINICAL RESEARCH

Oliver Wendell Holmes said that in Paris he learned three things from the great Louis: "Not to take authority when I can have facts, not to guess when I can know, and not to think a man must take physic because he is sick." These three principles are to be commended to every doctor as essential for true clinical research. Certainly no one should be satisfied to guess at the answer to any problem when it is possible to know, even though the solution requires some effort. And no matter how much any man may tower above his colleagues, his mere prestige does not make him infallible. The tremendous weight of Galen's authority kept the medical profession in the Dark Ages for more than a thousand years. But for the great force of Dupuytren's name—coupled, it must be confessed, with his brutality—appendicitis might have been recognized as a clinical entity when Melier first described it in 1827, nearly sixty years before Reginald Fitz's classic description of it was published. Fortunately the great Pasteur, in spite of his gentle nature, had enough native resolution under the surface successfully to oppose the die-hard authorities of his day and so to deserve the honor of fathering modern medicine.

Now, happily, while any new work is subject to keenly critical evaluation, we do not see the savage assaults on all new ideas or the jealous distrust of the younger members of the profession that prevailed in the days of Dupuytren and Pasteur. It is fortunate that new methods of diagnosis and treatment do have to run the gantlet of critical study; for thereby is the public protected from excessive enthusiasm, which Da Costa once said is "as dangerous as prejudice." It is true, however, that never in the world's history has the medical profession been so quick to assimilate and utilize new knowledge. In an incredibly short time, sulfanilamide has made a large place for itself. Just as soon as insulin could be standardized and placed on the market, it was being used all over the world. The value of liver in the treatment of pernicious anemia was speedily reflected in the soaring price of that hitherto humble article of diet. The serum treatment of pneumonia is being widely used and there is great interest in the exciting possibility that the x-rays may prove just as effective and far less taxing to the patient, physically as well as financially.

THE SHARING OF DISCOVERIES

One of the glories of the medical profession is that its members have no trade secrets. When any doctor, no matter whether a professor in a great medical school

or a general practitioner in an obscure rural section, makes a discovery that may benefit humanity, it is his duty to acquaint other doctors with it. With the multitude of medical journals now published, there is no valid excuse for any man to withhold any information he may have in return for what he learns from others. The two chief deterrents are false modesty and laziness.

Those who have read Marion Sims's fascinating story of his own life will recall his experience with his first published case report. He had operated for a double harelip and obtained such a remarkable result that a dental friend begged him to write a description for the *Journal of Dental Surgery*. When Sims objected that he had never written anything in his life, the dentist gave him the excellent advice "Write it as you would talk it, or as you have told it to me." When the journal with his article came, it was hidden behind some large books in his office. To his great dismay, some months later Dr. Ames, the leading practitioner of Montgomery and the most prolific writer, while on a social visit walked over to the bookcase, took down the volume that hid the dental journal, pulled it from its hiding place and began turning its leaves. Now let Dr. Sims [1] tell the story:

"I said to myself, 'My God! if he goes on in this way, he will come to the article on the "Lowndes County Girl's Harelip," and he will give me fits.' I was trembling like a leaf, as I stood there like a school boy. Still he stood there, turning over leaf after leaf, and, when he got to where the case was described, he did not look up at all, or say a word, but stood there, reading it down on the first page, then on the other page, deliberately reading it through. It just occupied two pages. My heart was in my throat. As he finished the article he stood perfectly still, and I also stood perfectly still, trembling. As he turned around I thought, 'I shall get it now.'

"In a moment he said, 'What would I give if I had the faculty of expressing myself in writing like that?' "

No doubt Dr. Sims was quite sincere in his description of the agony of embarrassment he suffered; yet he was well repaid by the commendation of his colleague. A far higher reward, however, was the feeling that he had added to human knowledge.

In contrast, let me tell a story of how a country doctor narrowly missed fame and—far more important—an opportunity to save thousands of children's lives. Last summer a loquacious old lady, well past three score and ten, told me that her old family physician, a Dr. Anderson, who died some years ago in Iredell County, lost his first baby of cholera infantum. When his next child reached the second summer, it acquired the same ailment, was desperately ill for a few days, then began improving. One day he came on the baby's old colored nurse feeding it scraped apple. He began to berate her soundly, asking why she wanted to kill this baby after he had already lost his firstborn. "Well, doctor," she replied, when he paused for breath, "your baby is getting better, isn't it?" When he admitted that it was, she continued, "That's because I've been feeding it scraped apple. If you want it to get well, please let me keep on." Grudgingly he had to admit the force of her argument and agreed for her to go on with the treatment. Within a few days the baby was well, and so long as he lived thereafter the good doctor used scraped apple regularly and successfully in diarrhea and dysentery. This was forty years before Birnberg published his first report in America of this now famous therapy. It is highly probable that Dr. Anderson's sense of modesty kept him from asking for a place on his medical society program or writing a report for a medical journal, in order to acquaint the world with his life-saving discovery; yet it was his duty to do so. He failed to obey the Scriptural command "Let your light so shine before men, that they may see your good works."

Laziness, I fear, is responsible for more sins of omission in recording our observations than is modesty; and by a process of rationalization it is easy to deceive oneself into thinking one is too modest to write when one is really too lazy. Every one who does any writing, even on a small scale, knows it is hard work; yet its difficulty is often exaggerated. The story is told of a cub reporter who had uncovered his first big story but was afraid he could not do justice to its news value. As he sat before his typewriter mopping his brow, a veteran noted his plight, walked over and, patting him on the shoulder, said "All you have to do, son, is to put down one little word after another." With a story to tell, any man with enough knowledge of the English language to get a medical diploma should be able to write it. The veteran reporter's wisdom was shown when he used the adjective "little" before "word." Oliver Wendell Holmes has aptly said "Never use a long word where a short one will serve the purpose. I know there are professors in this country who always 'ligate' arteries. Other surgeons only tie them, and it stops the bleeding just as well."

Soon after the "Life and Letters of Walter H. Page" was published, a friend gave me a copy at Christmas. While reading it, my 6 year old daughter came up behind me. She had been in the first grade four months and was anxious to use her new knowledge. "Daddy," she said, "let me see what I can read." For curiosity, I made a rough estimate of what she could understand and was surprised to find that she recognized about 70 per cent of the words used in one of Page's letters. I am not telling this story to show that I am the father of a child prodigy—God forbid!—but as proof that one of the world's greatest scholars ordinarily used words so simple that a first grade pupil could understand most of them. It helps us to clarify our own thoughts if we clothe them in the simplest language possible, and certainly it will help our readers to grasp them.

THE NEED OF RESEARCH

It is fortunate for many generations of his students as well as for his patients that the master clinician and teacher David Riesman [2] outgrew a youthful notion thus charmingly described by him: "A good many years ago a friend and I were . . . discussing the physical diagnosis of the heart. In our youthful ignorance we agreed . . . that it was a closed chapter, that all was known that ever could be known, and we had best devote our untapped energies in physical diagnosis to some other branch of medicine if we wanted to make discoveries. Little did we think that in a small provincial town in England a man at that very moment was blazing a new path in cardiac diagnosis, and that his work was to revolutionize a subject we

1. Sims, J. Marion: The Story of My Life, New York, D. Appleton Company, p. 215-216.

2. Riesman, David: High Blood Pressure and Longevity and Other Essays, Philadelphia, John C. Winston Company, p. 20.

believed to be perfect and unchangeable." In 1829 Andral wrote [2] "Since the publication of the immortal researches of Corvisart, and of numerous other works subsequent to his, which have still further enlarged the dominion of science, the history of diseases of the heart and its membranes is to be regarded as almost complete."

To any one who may feel that there is no further need for research, it is only necessary to suggest a few unsolved problems waiting for some Jenner, Pasteur, Banting or Minot: arthritis, asthma, hay fever, urticaria, migraine, epilepsy, peptic ulcer, spastic colitis, the common cold, sinusitis, granulopenia, essential hypertension, coronary heart disease, nephritis, ureteral stricture, encephalitis, much mental disease—and only too many others.

Doubtless the answer to many of our problems is as simple as was the liver treatment of pernicious anemia or the malarial treatment of dementia paralytica; yet it may be years before many of them will be solved. Others will require long, patient and persistent effort, in which some bit of keen observation by one of us may be as essential as the keystone to an arch. While occasionally an important discovery may be made by a brilliant flash of inspiration, far more are made by patient repetition of trial and error. Even the best will have more errors than successes; but the errors are soon forgotten while the successes are remembered. "We learn wisdom from failure much more than from success. We often discover what *will* do, by finding out what will not do; and probably he who never made a mistake never made a discovery" (Samuel Smiles).

The classic modern example of clinical research by a general practitioner is, of course, the research of Sir James Mackenzie. Soon after entering practice in the little Scotch village of Burnley he lost a young woman in childbirth from sudden heart failure. This harrowing experience made him resolve to learn all he could about heart disease, so that, if possible, he could avoid another such tragedy in the future. Finding little help in the literature available he began studying his patients themselves. For a score of years he kept accurate histories of all with cardiac irregularities. In order to record graphically the various types of pulse beats, he devised a crude but effective instrument for making pulse tracings on strips of smoked paper fastened to a revolving drum—a modification of the old Dudgeon sphygmograph, which he called the ink polygraph. At the end of twenty years he could say with authority which types of irregularity were dangerous and which were not. Then he began to publish the results of his study. First came a modest little volume called "The Study of the Pulse." Later he moved to London and published his monumental work, "Diseases of the Heart." He was literally forced into becoming a heart specialist and before his death was generally recognized as the one who had added more to our knowledge of the heart than any man since Harvey discovered the circulation.

Mackenzie had the great advantage, which he often emphasized, that he could follow his cases for periods of time impossible to those depending for clinical material on the floating population of a hospital or on the more unstable clientele of a city practitioner. He also often stressed the point that one could far more intelligently study one particular organ if one was familiar with the functions of the whole body.

Sir James used the same methods as did Hippocrates, who four centuries before Christ placed medicine on the highest plane it was to occupy until modern times. Instead of wasting his energy in useless speculation, Hippocrates studied every patient, recorded his observations, and compared results. It is an intriguing, though futile, speculation as to how many lives might have been saved had the medical profession followed his sane leadership instead of accepting as inspired the dogmatic statements of Galen. The really modern scientific method of observation taught and practiced by Hippocrates was forgotten in the blind worship of Galen's authority, and millions of lives were sacrificed on this altar.

One of the finest examples of surgical research by a general practitioner was that of J. Marion Sims. His prepared mind made one brilliant discovery after another; but his greatest "diligent protracted investigation for the purpose of adding to human knowledge" was learning to cure vesicovaginal fistula. While busy with a large general practice, he used all his spare time for four years in repeated operations on a few Negro slaves whom he kept at his own expense. One method after another failed. When his colleagues grew tired of assisting him, he trained the patients themselves to help. At length his family and friends begged him to give up a senseless undertaking before it ruined his practice and wasted all his financial resources. He persisted, however, and at long last the thirtieth operation on the Negro Anarcha was successful. In rapid succession others were cured of this distressing malady, and the foundation for the worldwide fame of Sims was laid. Years later he traveled abroad in a veritable triumphal march, operating in some of the most famous hospitals and on some of the most famous patients in Europe. He and other apparently tireless workers verify Matthew Arnold's definition of genius as "mainly an affair of energy" and the observation of Sir Joshua Reynolds that "If you have genius, industry will improve it; if you have none, industry will supply its place."

The temptation is to multiply examples, but time marches on and these are enough. I should like to tell of the numbers of papers read at various district meetings during the past year that showed the spirit of research. Some of the best came from small towns and rural communities. Rather than run the risk of discrimination, I shall not mention any by name. The past year has been one of the most profitable of my life, in that my travels over the state have afforded a continuous postgraduate course. Judging by the uniformly high order of the papers read in every district, the intelligence of the discussions, the eagerness of those attending the postgraduate courses and the spirit of research shown by so many of our men, the health of the people of North Carolina is in good hands.

O'Hanlon Building.

A Sick Pocketbook.—In other words, a sick pocketbook is more responsible for ill health than are certain supposed deficiencies in our system of providing medical care. These deficiencies can be corrected without disturbing the patient-physician relationship and without the injection of politically controlled third parties. In Pennsylvania, seventeen counties have had systems in operation which have proved to be efficient and economical. It is not necessary to build up elaborate departments to dispense medical services.—Borzell, Francis F.: The Medical Profession and the Social Worker, *Pennsylvania M. J.* **41**:683 (May) 1938.

SITES OF METASTASES FROM CARCINOMA OF THE ANUS, RECTUM AND SIGMOID COLON

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Except for a few individual reports, comparatively little has been written on the occurrence of metastases from malignant growths in the lower portion of the large bowel. For this reason, in order to discuss this subject on a factual basis, we have reviewed the records from the radiologic department of the Philadelphia General Hospital for the ten year period ending with 1936.

In 318, or 77.7 per cent, of a series of 409 cases of malignant process of the large bowel in which there was metastasis to one or more organs, as evidenced by biopsy, celiotomy, roentgenograms or necropsy, the primary site was in the anus, rectum or sigmoid colon. This confirms the observations of Larson and Nordland,[1] Heyd[2] and Rankin[3] that metastasis is encountered more frequently with malignant growths in these parts than with such growths in the upper portion of the large bowel. In our series the primary growth was located in the rectum in 239 cases, in the sigmoid in seventy-five and in the anus in four.

Much discussion has taken place concerning the relationship between the clinical type, the size of the growth and lymphatic metastasis.

Omitting the histologic types of tumors, one may say that, just as a papilliferous growth is less liable to become malignant than one that is sessile, so metastasis is encountered less frequently when a malignant growth protrudes into the lumen (papilliferous carcinoma) than when it invades the wall. This has been observed by Craig and MacCarty,[4] Dukes,[5] McVay[6] and Hayes.[7] In 267, or 80.8 per cent, of our series of 318 cases, the growth was described as sessile.

McVay[6] has shown that the size of the tumor cannot be relied on as an accurate index to the probable lymphatic involvement. Dukes expressed the opinion that there is no relationship between the surface area of the growth and the depth of penetration, because a large proliferating cancer may almost entirely occlude the lumen of the rectum yet be confined to the mucosa and submucosa, whereas a relatively small ulcerating lesion may have spread to invade the extrarectal tissue. In the series cited no attempt was made to measure the growth in the transverse or the longitudinal diameter, but it was observed that in all 267 cases at least three quarters of the circumference was involved.

This brings up several points for discussion. For instance, it has been observed that the spread of cancer of the rectum by continuity of tissue is a slow process. Handley[8] many years ago cited a case of rectal carcinoma in which, by staining of an entire section of bowel with mucicarmine, continuous spread was demonstrated in the submucosa beyond the gross limits of the tumor. He concluded that metastasis by this means occurs early and is frequent. Others, notably Cheatle,[9] Cole[10] and Monsarrat,[11] were unable to confirm these observations and concluded that this was a rare case. Leitch[12] went so far as to repeat the experiment, using mucicarmine in a considerable number of cancerous rectums, but failed to find stained cells in the submucosa except for those which he believed were the ganglionic cells of Auerbach's plexus. At any rate, spread by continuity of tissue is undoubtedly a slow process.

Lymphatic metastasis is more rapid; according to Miles[13] it occurs by means of the intramural lymphatic system and, after invading the external network, gives rise to extramural metastases long before the muscular coat has been penetrated by direct extension. Lockhart-Mummery,[14] on the other hand, expressed the opinion that invasion of the lymphatics occurs only after penetration of the muscular coat. Dukes[5] and Gordon-Watson[15] concurred in the belief that such invasion is not found until the cancer has spread by direct continuity through the rectal wall into the extrarectal lymphatics. Examination of serial sections of the involved rectal wall and contiguous and extrarectal tissues was not possible in this series of cases.

No attempt was made to determine the duration of the growth by computing the period between the date on which the lesion was first recognized and the time at which metastasis became apparent. We did employ a less accurate method, that of adding six months to the period between the onset of symptoms and the time at which both local and remote metastases were noted. As previously reported,[16] the average period from the onset of symptoms to recognition of the cancer in 1,031 of a possible 1,995 cases was nine months and three weeks. In this series of 318 cases, the average period between the onset of symptoms and the observation of extension or regional metastasis was eleven months and two weeks, whereas the average period between the onset of symptoms and observation of distant metastases (lungs, pancreas, vertebrae, spleen, renal capsule and heart) was nineteen months. If six months is added to each figure, the growths showing regional metastases had existed for seventeen months and two weeks, while those showing distant metastases had existed for twenty-five months. This closely parallels the estimated period of duration as expressed by Miles,[17] in that growths involving three quarters of the circumference of the intestine had existed eighteen months or longer, for it will be recalled that they had done so in 267 cases of our series.

From the Department of Radiology, Philadelphia General Hospital.
Read before the Proctologic Society of the Graduate Hospital, University of Pennsylvania, March 9, 1938.

1. Larson, L. M., and Nordland, Martin: Malignant Tumors of the Large Intestine, Ann. Surg. **100**: 328 (Aug.) 1934.
2. Heyd, C. G.: Malignancies of the Rectum and Rectosigmoid, Am. J. Surg. **38**: 230 (Nov.) 1937.
3. Rankin, F. W., and Fortune, C. H.: Metastasis to Thyroid Gland, Ann. Surg. **104**: 36 (July) 1936.
4. Craig, W. McK., and MacCarty, W. C.: Involvement of the Lymph Glands in Carcinoma of the Cecum, Ann. Surg. **77**: 698 (June) 1923.
5. Dukes, Cuthbert: Classification of Cancer of the Rectum, J. Path. & Bact. **35**: 323 (May) 1932.
6. McVay, J. R.: Involvement of Lymph Nodes in Carcinoma of Rectum, Ann. Surg. **76**: 755 (Dec.) 1922.
7. Hayes, J. M.: The Involvement of the Lymph Glands in Carcinoma of the Large Intestine, Minnesota Med. **4**: 653 (Nov.) 1921.
8. Handley, W. S.: The Dissemination of Rectal Carcinoma, Brit. M. J. **1**: 584 (March) 1913; **1**: 197 (April) 1910.
9. Cheatle, G. L.: The Spread of Cancer in the Lower Part of the Large Intestine, Brit. M. J. **1**: 303 (Feb. 7) 1914.
10. Cole, P. P.: The Intramural Spread of Rectal Carcinoma, Brit. M. J. **1**: 43 (March 1) 1913.
11. Monsarrat, K. W., and Wilhaus, I. J.: Intramural Extension in Rectal Cancer, Brit. J. Surg. **1**: 173, 1914.
12. Leitch, A., cited by Miles.[13]
13. Miles, W. E.: Cancer of Rectum, London, Harrison & Sons, 1926.
14. Lockhart-Mummery, J. P.: Diseases of the Rectum and Colon, ed. 2, Baltimore, William Wood & Co., 1934, p. 311.
15. Gordon-Watson, Charles, and Dukes, Cuthbert: Treatment of Carcinomas of the Rectum with Radium, with Introduction on Spread of Cancer of the Rectum, Brit. J. Surg. **17**: 643 (April) 1930.
16. Bacon, H. E.: The Anus, Rectum and Sigmoid Colon, Philadelphia, J. B. Lippincott Company, 1938; Experimental Studies in Proctology, J. M. World **52**: 617 (Nov.) 1934.
17. Miles, W. E.: The Pathology of the Spread of Cancer of the Rectum and Its Bearing upon the Surgery of the Cancerous Rectum, Surg., Gynec. & Obst. **52**: 350 (Feb.) 1931.

The distribution as to age, sex and race is shown in table 1, and the sites of metastasis and local extension (in order of their frequency) are listed in table 2. Other sites of metastatic involvement not found in this series have been reported; they include the umbilicus,[18] ureter,[19] eye,[20] humerus,[21] clavicle,[22] sternum,[23] radius,[23] ulna [23] and supraclavicular nodes.[24]

TABLE 1.—*Distribution as to Age, Sex and Race*

Age	Number	Sex	Number	Race	Number
10-20	1	Males	202	White	309
21-30	13	Females	116	Negro	8
31-40	36			Chinese	1
41-50	35				
51-60	85				
61-70	92				
71-80	52				
81-90	4				

A few decades ago Mayo [25] and McArthur [26] observed that the liver is usually the first remote organ affected. Pruitt [27] has estimated the frequency of hepatic metastasis to be 40 per cent, and while our percentage is similar to this it must be remembered that this report is based only on cases in which there was metastasis. So far as metastasis to lymph nodes is concerned, the large series of 1,112 cases reported by Buday [28] and Reichelmann [29] is worthy of mention. As cited by Pennington,[30] these two authors found involvement of the regional lymph nodes in 336 cases, or 30 per cent, and of the distant nodes in sixty cases, or 5.3 per cent.

Bargen and Larson [20] in a series of 260 cases noted the following involvement (verified by microscopic examination in 113, or 43.4 per cent): perirectal, seventy-one cases; mesenteric, fifteen; inguinal, fourteen; iliac, five; aortic, five; axillary, two, and omental, one.

Compared with these figures, the percentage of regional glandular involvement in our series is low (31.1). It should be remembered, however, that all the regional nodes were not removed or examined in each individual case. Quite recently, Brown and Warren [31] found that in twenty-four, or 34 per cent, of seventy cases in which there was visceral metastasis, the lymph nodes failed to show involvement.

Aufses [21] confirmed von Recklinghausen's [32] order of metastasis to bone from carcinoma of the rectum as follows: vertebra, femur, ribs, skull, sternum, humerus, pelvis, sacrum, radius, scapula and ulna. In our series of cases, however, the order of frequency was sacrum, coccyx, pelvis, lumbar vertebra, dorsal vertebra, femur, ribs, skull, cervical vertebra and shoulder girdle.

Rankin [33] and Broders [34] observed a parallelism in the ratio of glandular involvement and the grade of malignancy and also that the absence of metastasis increases in inverse ratio to the grade of the malignancy.

The grade of the tumor and its relationship to metastasis in 260 of 560 cases of rectal carcinoma as cited by Broders [35] are as follows: eighty-two cases (14.65 per cent) of grade 1 cancer, with metastasis in 26.82 per cent; 290 cases (51.78 per cent) of grade 2 cancer, with metastasis in 44.13 per cent; 137 cases (24.6 per cent) of grade 3 cancer, with metastasis in 56.2 per cent, and fifty-one cases (9.1 per cent) of grade 4 cancer, with metastasis in 64.7 per cent.

These figures are consistent with those of Karsner and Clark,[36] except for grade 1: two cases of grade 1 cancer, with metastasis in 100 per cent; twelve cases of grade 2 cancer, with metastasis in 75 per cent; seventeen cases of grade 3 cancer, with metastasis in 76 per cent, and seven cases of grade 4 cancer, with metastasis in 100 per cent.

On the other hand, in our series of 318 cases, in all of which there was metastasis, the grade of tumor according to Broder's classification was noted as follows: twenty-one cases, or 6.6 per cent, grade 1 cancer; 165 cases, or 51.9 per cent, grade 2; 117 cases, or 36.8 per cent, grade 3, and nine cases, or 2.8 per cent, grade 4. In six, or 1.9 per cent, the grade was not stated.

It is apparent that there is a vast difference in the series, which in itself deserves some explanation. It must be remembered that, first, several pathologists have reported on the gradings and, secondly, only a few specimens were examined serially. The second factor is important because we know that the arrangement and the differentiation of the malignant cells of rectal carcinomas are not uniform throughout the growth. It may also be mentioned, as in the cases cited by Dukes,[5] that fragments removed for diagnosis differed in grade from the specimens excised at operation. Dukes noted also considerable discrepancy between the grade according to cell differentiation and the extent of spread. In discussing malignancy of the breast, Pfahler quoted Dawson and Tod [37] as follows: "These microscopic

TABLE 2.—*Sites of Metastasis and Local Extension*

Site	Number of Patients	Percentage	Site	Number of Patients	Percentage
Liver	128	40.0	Diaphragm	3	0.9
Regional glands	99	31.1	Lumbar vertebra	3	0.9
Peritoneum	59	18.6	Dorsal vertebra	3	0.9
Lungs	47	14.7	Broad ligament	3	0.9
Bladder	27	8.5	Heart (epicardium)	2	0.6
Sacrum	22	6.9	Thyroid	2	0.6
Coccyx	18	5.7	Femur	2	0.6
Uterus	14	4.4	Ribs	2	0.6
Pancreas	11	3.5	Skull	2	0.6
Renal capsule	9	2.8	Buttocks	2	0.6
Prostate	8	2.5	Breast	1	0.3
Vagina	8	2.5	Duodenum	1	0.3
Spleen	7	2.2	Cervical vertebra	1	0.3
Inguinal glands	6	1.9	Shoulder girdle	1	0.3
Pelvis	5	1.6	Brain	1	0.3
Perineum	4	1.3	Testicle	1	0.3
Vulva	4	1.3	Mediastinum	1	0.3
Ovaries	4	1.3			

18. Warner, F.: Carcinoma of the Umbilicus, Surg., Gynec. & Obst. **27:** 204 (Aug.) 1918.
19. Rabs, M.: Bull. Soc. Anat. **1:** 106 (Jan.) 1898.
20. Bargen, A. J., and Larson, L. M.: The Mode of Spread of Carcinoma of the Rectum, Minnesota Med. **16:** 478 (July) 1933.
21. Aufses, A. H.: Skeletal Metastases from Carcinoma of the Rectum, Arch. Surg. **21:** 916 (Dec.) 1930. Hayden.[22] Pennington.[30] von Recklinghausen.[32]
22. Hayden, E. P.: Cancer of the Rectum and Sigmoid, New England J. Med. **214:** 401 (Feb. 27) 1936.
23. Aufses.[21] von Recklinghausen.[32]
24. Simon, G.: Bull. Soc. Anat. **2:** 211 (Feb.) 1900.
25. Mayo, W. J.: Removal of the Rectum for Cancer, Ann. Surg. **51:** 854 (June) 1910.
26. McArthur, S. S.: Carcinoma of the Rectum, Surg., Gynec. & Obst. **21:** 495 (Oct.) 1915.
27. Pruitt, M. C.: Modern Proctology, St. Louis, C. V. Mosby Company, 1931, p. 305.
28. Buday, K.: Ztschr. f. Krebsforsch. **6:**1, 1908; quoted by Pennington.[30]
29. Reichelmann, W.: Berl. klin. Wchnschr. **39:**723, 1902; cited by Pennington.[30]
30. Pennington, R. W.: Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Co., 1923.
31. Brown, C. E., and Warren, Shields: Visceral Metastasis from Rectal Carcinoma, Surg., Gynec. & Obst. **66:** 611 (March) 1938.
32. von Recklinghausen, cited by Karsner and Clark.[36]
33. Rankin, F. W., and Broders, A. C.: Factors Influencing the Prognosis in Carcinoma of the Rectum, Tr. South. S. A. **40:** 133, 1927.
34. Broders, A. C.: The Grading of Carcinoma, Minnesota Med. **8:**726 (Dec.) 1925; Carcinoma Grading and Practical Application, Arch. Path. & Lab. Med. **2:** 376 (Sept.) 1926.
35. Broders, A. C.: The Grading of Cancer: Its Relationship to Metastasis and Prognosis, Texas State J. Med. **29:** 520 (Dec.) 1933.
36. Karsner, H. T., and Clark, Burton, Jr.: Analysis of 104 Cases of Carcinoma of the Large Intestine, Am. J. Cancer **16:** 958 (Sept.) 1932.
37. Dawson, E. K., and Tod, M. C.: Prognosis in Mammary Carcinoma in Relation to Grading and Treatment, Edinburgh M. J. **41:** 61 (Feb.) 1934; cited by Pfahler, G. E.: The Treatment of Carcinoma of the Breast, Am. J. Roentgenol. **39:** 1 (Jan.) 1938.

grades of malignancy can only be determined after complete operation and study of the entire breast. While there is a general microscopic appearance in these tumors which permits classification . . . some characteristics of all these grades are apt to be found in some part of each tumor." Reimann [38] remarked: "The various grades of malignancy can be found in at least half the tumors encountered in a series such as we have at our hospital and probably 75 per cent if sufficient number of sections are taken from different areas." MacCarty [39] stated that different portions and even different areas in the same microscopic field show a different grade; the grades of the primary and of the secondary tumor vary; recurrent tumors are often different in grade from the primary tumor, and different grades have different criteria.

In comparing the grade of cancers in the upper and in the lower portion of the large bowel, Karsner and Clark [36] noted a much higher incidence of grades 3 and 4 in the former location. In our series there were 409 cases of malignant growth in the large bowel with metastasis; in 318 the process was in the anus, rectum or sigmoid colon and in eighty-one in the upper portion of the large bowel. In fifty-two of these eighty-one cases the grade of cancer according to Broders' classification was reported; in twenty-eight, or 53.8 per cent, the cancer was of grade 2; in sixteen, or 30 per cent, it was of grade 3, and in eight, or 15.4 per cent, it was of grade 4.

SUMMARY

In 318, or 77.7 per cent, of a series of 409 cases of malignant growth in the large bowel, in all of which there was metastasis, the primary site was in the rectum, sigmoid colon or anus.

In 267, or 80.8 per cent, the tumor was described as sessile. In the 267 cases, regardless of the type of tumor, approximately three quarters of the circumference of the bowel wall was involved.

In 318 cases the average period between the onset of symptoms and the observance of regional metastasis was seventeen months and two weeks, whereas the average period between the onset of symptoms and the observance of distant metastasis (e. g., to the liver or lung) was twenty-five months.

The greatest number of cases of primary cancer of the large bowel occurred during the fifth, sixth and seventh decades, men being more frequently affected than women.

Visceral metastasis was most prevalent in the liver, ranking first, with 40 per cent; metastasis to regional lymph nodes came next, with 31.1 per cent; with bony metastasis, the order of frequency was sacrum, coccyx, pelvis, lumbar vertebrae and so forth.

According to Broders' classification, in the greatest number of cases in our series, in all of which there was metastasis, the cancer was of grade 2 (51.9 per cent). In 36.8 per cent it was of grade 3.

CONCLUSIONS

Metastasis is more frequently encountered with a malignant growth in the lower portion of the large bowel than with such a growth in the upper portion.

Sessile growths are more prone to metastasize than papilliferous growths.

There is a period of approximately eight months between the first recognition of the tumor and the observance of regional and distant metastasis.

We were unable to support the contention that the percentage of metastases always is greater for the higher grades of malignancy.

Our studies show a predominance of grade 2 tumors.

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38. Reimann, cited by Pfahler, G. E.: The Treatment of Carcinoma of the Breast, Am. J. Roentgenol. **39**: 1 (Jan.) 1938.
39. MacCarty, W. C.: Cytologic Diagnosis of Neoplasms, J. A. M. A. **81**: 519 (Aug. 18) 1923.

THROMBOCYTOPEN

A SUBSTANCE IN THE EXTRACT FROM THE SPLEEN OF PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA THAT REDUCES THE NUMBER OF BLOOD PLATELETS

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AND
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The purpose of this article is to describe more fully an extract obtained from the spleen of patients suffering from idiopathic thrombocytopenic purpura which reduces the number of platelets in the circulating blood. A brief preliminary report has already been published.[1] All the material was obtained through the cooperation of Dr. Dean Lewis, who felt that it might be possible to make extracts of such a nature that the clinical picture of the disease could be reproduced experimentally.

MATERIAL AND METHOD

Chronologically, the first successful extract was made from the spleen of a patient, the essential points in whose case are as follows:

CASE 1.—M. O., a white woman, aged 22, was admitted to the Johns Hopkins Hospital on Jan. 25, 1937, because of rectal bleeding. The family history revealed no excessive bleeding or blood dyscrasia. She was first admitted to the hospital in 1933, at which time an appendectomy was performed. The operation and convalescence did not indicate a hemorrhagic tendency. The early history did not suggest any tendency to excessive bleeding. The menstrual history was normal, with each period lasting for three to four days and only moderate flow. In August 1936, during the fourth month of her first pregnancy, the patient noted spontaneous bleeding from the gums in small amounts. In November some small purpuric areas were noted on the abdomen, but they disappeared in two days. These purpuric spots continued to appear at weekly intervals throughout the remainder of the pregnancy. Blood studies showed normal cell counts. On December 18 a blood smear showed the number of platelets to be greatly reduced. A rectal examination in the Obstetrical Dispensary on Jan. 25, 1937, caused excessive bleeding, and the patient was admitted to the hospital. Two hundred cc. of blood and 0.6 cc. of snake venom were given on the day of admission and again on the following day. On January 27 she was delivered of a normal child, with hemorrhage estimated to be only 150 cc. Blood studies on the day of delivery showed platelets 78,000 and red cells 4,000,000 per cubic millimeter, hemoglobin content 12 Gm., bleeding time eight minutes and reaction to the tourniquet test positive. Some vaginal bleeding began on February 1 and continued for a month, during which time purpuric spots again appeared on the abdomen. On March 1 large clots of blood were passed, and this form of hemorrhage continued until April 8. From March 12 to March 19, three blood trans-

From the Surgical Hunterian Laboratory of the Johns Hopkins University School of Medicine.

1. Troland, C. E., and Lee, F. C.: A Preliminary Report on a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura, Bull. Johns Hopkins Hosp. **62**: 85 (Jan.) 1938.

fusions were given, as well as four injections of snake venom in doses varying from 0.6 to 1 cc. Bleeding did not stop. The platelet count remained around 36,000, and the hemoglobin content dropped from 12 to 5.8 Gm. On April 8 splenectomy was performed by Dr. Paul A. Kunkel. Vaginal bleeding ceased, and blood studies on April 20 showed the platelet count to be 280,000, bleeding time one and one-half minutes, red cells 4,170,000, clotting time nine minutes and clot retraction time one hour. The patient was discharged on April 22. Blood studies on May 12 showed the platelet count to be 112,000, bleeding time four minutes, clotting time seven minutes, clot retraction time forty-five minutes and hemoglobin content

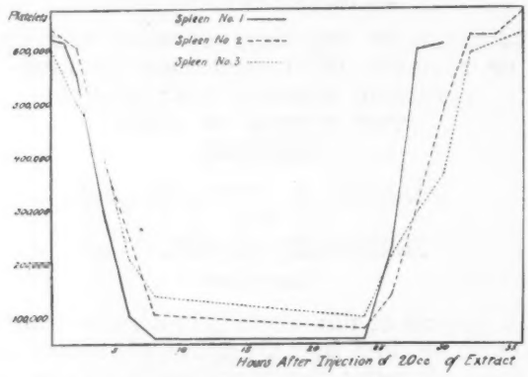

Chart 1.—The fall and subsequent rise to normal of the number of platelets in the circulating blood of a rabbit after the intravenous injection of 20 cc. of splenic extracts obtained from three patients with idiopathic thrombocytopenic purpura.

13 Gm. She was readmitted on May 25, complaining of pain in the right upper quadrant, which was diagnosed as due to acute cholecystitis. She was discharged on May 27. Since the splenectomy there has been no evidence of excessive bleeding.

The spleen weighed 120 Gm. and was smooth, soft and glistening. Microscopic examination revealed conspicuous malpighian bodies but only occasional germinal centers. The sinuses were partly filled with blood. There were no abnormal cells in the pulp, and there was little evidence of blood destruction.

The spleen was cut up and placed in five volumes of acetone. Dr. Arthur Grollman suggested that reagent acetone be used and not the commercial variety. The specimen was shaken occasionally from the time of removal on April 8 until June 4, when the acetone, which by that time was a light orange, was filtered off. Commercial acetone was put back on the ground-up spleen, primarily to preserve it but also with the idea of seeing whether this type of acetone could be used for extraction.

The filtered acetone from the first extraction was distilled off, leaving a brownish sediment on the walls and bottom of the balloon flask. One hundred cc. of distilled water was poured into the flask and shaken vigorously in order to take up as much as possible of the brown residue. The cloudy brown fluid was filtered through filter paper, and the small amount of fatty dark brown material remained on the paper. The filtrate was cloudy and orange-brown. It was put on the ice at once and never showed a precipitate.

Before any tests were made of the first extract, and therefore without its being known whether the acetone extract was of any value, the spleen from the second patient with thrombocytopenic purpura was received. The essential features of this patient's history are as follows:

CASE 2.—F. D., a white girl, aged 14 years, was first seen in the Harriet Lane Home of the Johns Hopkins Hospital in 1923, when 3 months of age. The family history revealed no excessive bleeding or blood dyscrasia. A hard purple swelling had appeared on the right side of the face at the age of 6 weeks and had gradually grown to include the right ear and the right side of the neck. She was referred to the Howard A. Kelly Hospital, where radium treatments were given for one and a half years. The purple area disappeared completely. During the next seven years she had the usual childhood diseases, measles, pertussis and chickenpox. In 1930 a tonsillectomy and an adenoidectomy were performed without excessive bleeding. The menses first appeared in February 1936, with profuse bleeding, and coincidentally with their appearance the purple mass on the face and neck reappeared. Radium treatments were again resorted to, and the mass promptly disappeared. On October 19, five days before the onset of menstruation, the purple swelling reappeared, but it disappeared when menstruation began. This same phenomenon recurred in three week cycles, and during the period of greatest swelling there was some respiratory embarrassment, which became pronounced on December 30, and she was admitted to the hospital.

Examination showed the right side of the face and neck to be greatly swollen, and there were extensive hemorrhages into both eyelids and from the buccal mucous membranes. Difficulty in breathing was moderately severe but not enough to justify tracheotomy. Blood studies showed the platelet count to be 198,000 per cubic millimeter, the reaction to the tourniquet test positive, red cells 4,360,000 and hemoglobin content 13.8 Gm. Diagnoses of hemangiosarcoma of the face and thrombocytopenic purpura were made. The patient's condition gradually improved, and she was discharged on Feb. 12, 1937. She was readmitted on February 22, because of respiratory difficulties caused by the swelling of the right side of the face and neck. Blood studies showed the platelet count to be 128,000, but extravasation of blood around the venous puncture needle prevented further studies. She was discharged on March 7 but was again readmitted on March 19. Seven days after discharge she had received a blow on her ankle; a marked extravasation of blood promptly appeared. Her gums bled spontaneously. Blood studies on March 19 showed platelets 21,000 and red cells 4,680,000 per cubic millimeter, bleeding time thirty minutes, clotting time five minutes, clot retraction time twenty-four hours and reaction to the tourniquet test positive. Her condition improved and she was discharged on May 6.

On June 11 the patient was readmitted, with identical complaints. Splenectomy was performed by Dr. Barnes Woodhall on June 28. A small accessory spleen was found and removed. Blood studies on July 7 showed bleeding time three and one-half minutes, clotting time eight minutes, platelet count 245,000 per cubic millimeter. She was discharged on July 26 but readmitted on August 8 because of respiratory difficulty following recurring swelling of the right side of the face and neck. Her condition again improved, and she was discharged on August 23 after having been given two transfusions. On September 3 the swelling of the neck became pronounced and breathing difficult. On the following day there were epistaxis and progressive respiratory embarrassment. The patient died on September 4 after tracheotomy.

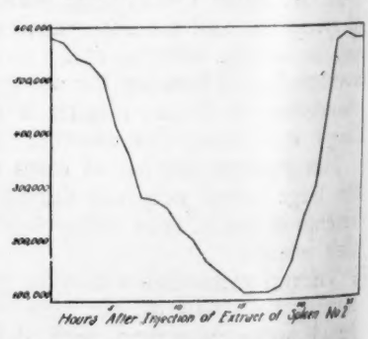

Chart 2.—The hourly change in the number of platelets in the circulating blood of a rabbit after the intravenous injection of 3 cc. of a splenic extract obtained from a patient with idiopathic thrombocytopenic purpura.

The spleen weighed 131 Gm. and was smooth and glistening. It was moderately tense on section. Microscopic examination showed marked fibrosis and a scarcity of cells in the pulp. Malpighian bodies were conspicuous, but only rarely were germinal centers seen. Numerous vessels showed hyaline changes, and there was a suggestion of the sickle cell trait. The accessory spleen showed marked hyaline changes in the vessels.

On the day of splenectomy, June 28, 1937, the spleen was ground up in a food chopper and, again empirically, placed in reagent acetone, as was the first spleen.

At this time no tests with the extract from the first spleen had been carried out, but extensive control platelet counts had been made in order to insure uniformity and reliability of the technic. The direct method of counting platelets was utilized throughout, the fluid of Rees and Ecker being used and the indirect blood smear method being employed for frequent checks on the direct counts.

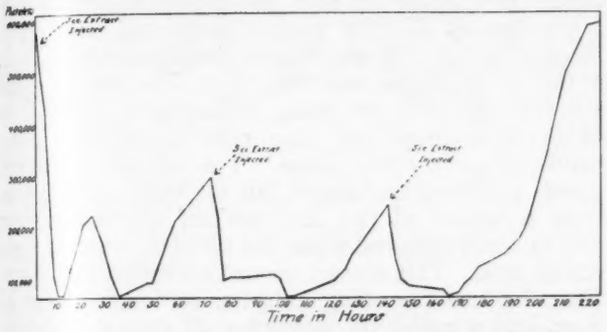

Chart 3.—The effect on the number of platelets in the circulating blood of a rabbit of repeated intravenous injections of a splenic extract obtained from a patient with idiopathic thrombocytopenic purpura.

On July 16 the first injections of the acetone extract from the spleen of patient 1 were made. A stock rabbit was used as the test animal, primarily because of simplicity and convenience. In all cases a new rabbit was used for each injection. After the normal control platelet count was made, 5 cc. of the first extract, known as S-1, was injected into the marginal vein of the ear of this rabbit, which weighed 2 Kg. When no untoward reaction occurred in five minutes, 15 cc. more of the same extract was injected into the same vein. The platelets steadily fell from their preinjection level of 620,000 per cubic millimeter to 58,000 in eight hours (chart 1). At this low level of platelets it was noted that bleeding was difficult to check when the ear was stuck. No purpuric spots, however, were noted at any time. The platelet count twenty-four hours after injection was 58,000 per cubic millimeter, but it rapidly rose in six hours to 610,000.

On July 27 an injection of 14 cc. of the same extract, S-1, was made into the marginal vein of the ear of a second rabbit, which weighed 2.2 Kg. The platelet count fell from the preinjection level of 612,000 per cubic millimeter to 96,000 in eight hours. The platelet count twenty-four hours after injection was 100,000 and rapidly rose to 605,000 in eight hours. It was again noted that bleeding was difficult to control when the platelet count was low, and again no purpuric areas were noted.

The commercial acetone that had been put on the spleen when the first reagent acetone was filtered off was now filtered and distilled, forming extract S-1-B. On September 14, 20 cc. of this extract was injected into a rabbit. The platelet count fell from 620,000 per cubic millimeter to 580,000 in six hours and rapidly rose to normal. This lack of potency might have been due to the use of commercial acetone instead of reagent acetone but was probably due to the fact that virtually all the platelet-reducing substance had been extracted by the first treatment with acetone.

The extract from the second spleen was prepared by a method identical with that used in the first case. The spleen was ground up in a food chopper immediately after operative removal on June 28 and placed in reagent acetone. The acetone was distilled off on October 8, and 100 cc. of distilled water was added. This extract, S-2, also was always kept in the ice box.

On October 12, 20 cc. of this extract was injected into the marginal vein of the ear of a rabbit weighing 2.1 Kg. The platelet count fell from the preinjection level of 640,000 per cubic millimeter to 70,000 in twenty-four hours and rose to the preinjection level by the end of thirty-six hours (chart 1). In order to determine the minimal effective dose of the extract, 3 cc. was injected into a rabbit weighing 2.1 Kg. on October 18. The platelet count fell from a preinjection level of 640,000 to 80,000 in twenty-four hours and rose to normal in thirty-two hours (chart 2). A smaller dose had little effect on the platelet count.

On October 25, 5 cc. of the extract S-2 was injected into the marginal vein of the ear of a rabbit weighing 1.9 Kg. after control studies had shown the platelet count to be 580,000 per cubic millimeter, the red count 4,750,000, the white cell count 6,000 and the bleeding time two minutes. The platelet count fell to 70,000 in ten hours, but the red and white cell counts showed no appreciable change. The bleeding time, however, increased to four and one-half minutes. The platelet count was kept low for nine days, three additional injections of the extract being made when the count began to rise (chart 3). When the platelet count was low, around 70,000 per cubic millimeter, further studies showed the clotting time to be eight minutes and clot retraction not complete until twenty-four hours. The fragility of the red cells was within normal range.

In order to obtain further knowledge of the characteristics of the extract, 8 cc. was boiled for three minutes and then injected into a rabbit weighing 2 Kg. The platelet count fell from a preinjection level of 580,000 per cubic millimeter to 147,000 in twelve hours and rose again to normal in thirty-six hours. This test would seem to indicate that the substance producing thrombocytopenia is partly thermostabile and would suggest in addition that its nature is possibly that of a protein.

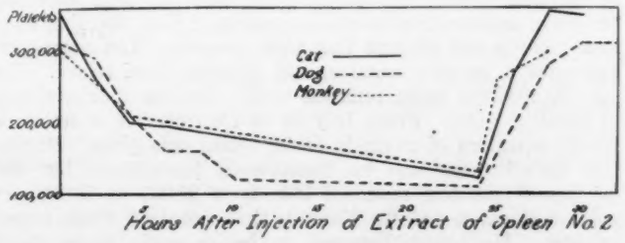

Chart 4.—The changes in the number of platelets in the circulating blood of a cat, a dog and a monkey after the intravenous injection of a splenic extract obtained from a patient with idiopathic thrombocytopenic purpura.

Since the rabbit had been the test animal so far, it was decided to check these results on other laboratory animals. Accordingly, on November 16, 5 cc. of the extract S-2 was injected into the left external jugular vein of a cat weighing 3.2 Kg. The platelet count fell from a control level of 350,000 per cubic millimeter to 120,000 in twenty-four hours and then rapidly rose to normal in six hours. On the same day 5 cc. of the extract was injected intravenously into a dog weighing 7.2 Kg. The platelet count fell from a preinjection level of 310,000 to 110,000 in twenty-four hours and rose again to normal in seven hours. On November 19, 10 cc. of the extract was injected intravenously into a

monkey weighing 8.8 Kg. The platelet count again fell from a control level of 300,000 per cubic millimeter to 120,000 in twenty-four hours and then returned to normal in five hours (chart 4).

On Jan. 25, 1938, 3 cc., which represented the last of extract S-2, was injected into a rabbit, and a platelet count was made at hourly intervals. The control count was 580,000; the lowest count was 100,000, at fourteen hours, and the normal level was attained in twenty-four hours (chart 4). The fact that the platelet count did not fall so rapidly and did not remain low for a longer time might well be explained by the age of the extract.

On Oct. 18, 1937, patient E. K. entered the hospital for splenectomy to be performed on the following day. One hour before he went to the operating room 20 cc. of his blood was taken and immediately injected into the aural vein of a rabbit, but there was no fall in the platelet count of the animal's blood. The animal was found dead at the end of eight hours.

CASE 3.—E. K., a white youth, aged 19, was admitted to the Johns Hopkins Hospital on Oct. 18, 1937, with the complaint of excessive bleeding. The family history showed no excessive bleeding or blood dyscrasia. He was first seen in the Harriet Lane Home in 1925, when 7 years old, suffering from nephritis following pneumonia. On Aug. 19, 1925, he complained of severe abdominal pain and vomited blood. A diagnosis of Henoch's purpura was made. On October 25 he was again seen because he had been bleeding for two weeks from a bruised finger. A blood smear showed virtually no platelets. When

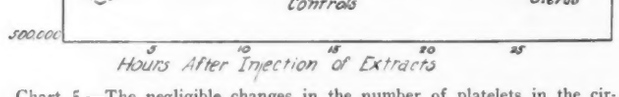

Chart 5.—The negligible changes in the number of platelets in the circulating blood of a rabbit after the intravenous injection of three representative control extracts.

6 years of age he bruised himself in a fall, and after that time he noted that he always bruised easily. Circumcision was performed when he was 13, with profuse hemorrhage for two days. On Nov. 7, 1935, he came to the hospital complaining of bleeding gums. Blood studies showed red cells 4,890,000 per cubic millimeter, hemoglobin content 15 Gm., bleeding time four minutes and clotting time eight minutes. The tourniquet test gave a positive reaction, and platelets were scarce. On July 8, 1936, he again returned to the dispensary complaining of bleeding gums. From July 14 to December 30 a series of fifteen injections of moccasin snake venom was given. During this period there was no spontaneous hemorrhage but the number of platelets remained low, from 22,000 to 70,000 per cubic millimeter, and the bleeding time remained about fifteen minutes. He began, however, to bruise easily again about Jan. 6, 1937, and seven roentgen treatments, directed primarily at the spleen, were given in three weeks, but to no avail. Blood studies on October 18 showed the platelet count to be 38,000 and the bleeding time to be ten minutes. A splenectomy was performed on October 19 by Dr. P. A. Kunkel, and blood studies on the following day showed the platelet count to be 84,600, bleeding time one and one-half minutes, clotting time four minutes and clot retraction time one hour. The platelets rose steadily to 810,000 by November 3. On November 5 the patient was admitted to the hospital with the complaint of pain in the left costovertebral angle, and a provisional diagnosis of an embolus to a radicle of the left renal artery was made. He was discharged asymptomatic on November 14. There was no return of bleeding, and on November 17 the platelets numbered 470,000.

The spleen weighed 127 Gm. and was small, smooth and glistening. Microscopic examination revealed a large number of splenic corpuscles, some of them having germinal centers. Many sinuses were dilated. The pulp appeared normal, and there was no increase in cellular elements. The arterioles of the corpuscles were extremely sclerotic.

The extract from this spleen was prepared by a method identical with that in the two preceding cases. The spleen was ground up immediately after its surgical removal, on October 19, and put in 255 cc. of reagent acetone. The acetone was filtered and then distilled off on October 25, and 100 cc. of distilled water was added to the remaining extract. This extract also was always kept in the ice box, and it was known as S-3.

On October 27, after control counts had been made, 20 cc. of this extract was injected into the marginal vein of the ear of a rabbit weighing 2 Kg. The platelet count fell from 605,000 per cubic millimeter to 100,000 in twenty-four hours and then rose to 605,600 in an additional twenty-four hours. The red and white cell counts remained unchanged, but the bleeding time rose from a control of two and one-half minutes to four and one-half minutes when the platelets were at their lowest level. This extract seemed somewhat less potent than the two preceding extracts, as the injection of 5 cc. into a rabbit on November 22 caused a platelet drop from 600,000 only to 340,000 per cubic millimeter.

On November 25 an attempt was made to see whether massive doses of the extract would remove still more platelets from the blood; accordingly, 40 cc. of the extract was injected into a rabbit weighing 2.2 Kg. and having a platelet count of 602,000. The platelets, however, reached their lowest level at 100,000 per cubic millimeter, after six hours, and returned to normal values in thirty hours.

As soon as the first spleen extract showed an ability to reduce the number of platelets, control tissue was looked for, and curiously enough the most desirable tissue, a normal spleen, was the last specimen to be obtained. The experiences with the control series are chronologically arranged.

The first control extract was prepared from one lobe (weight 110 Gm.) of a thyroid gland removed for hyperthyroidism. The gland was removed on July 28, 1937, and was immediately ground up and put in acetone. The acetone was distilled off and distilled water added to the residue on August 20. On August 30, 20 cc. of the extract known as S-6 was injected into a rabbit weighing 2 Kg. The platelet count fell from 560,000 per cubic millimeter to 540,000, a change scarcely outside the range of experimental error.

The second control extract was prepared from a myomatous uterus weighing 500 Gm. The specimen was removed at operation on July 29, 1937, and the usual preparation was carried out, the acetone being distilled off on August 11. Twenty cc. of this extract, known as S-5, was injected into the vein of the ear of a rabbit weighing 2.2 Kg. on August 23. The platelet count fell from a preinjection level of 600,000 to 580,000 in four hours and had regained normal limits within another four hours (chart 5).

The third control extract was prepared from one half of the spleen removed from a patient having Banti's disease. The spleen was removed on October 19, prepared and put in acetone in the usual manner, and the acetone was distilled off on October 27. Twenty cc. of this extract injected into a rabbit on November 12 caused a fall in the platelet count from 580,000 per cubic millimeter to 550,000 in four hours, with a rise to 581,000 in an additional four hours (chart 5).

The fourth control extract was prepared from the spleen of a patient suffering from congenital hemolytic jaundice. The specimen was obtained at operation on July 27, 1937, and prepared by the usual method, the acetone being distilled off on October 19. The injection of 20 cc. of this extract into a rabbit on November 12 caused a fall in the platelet count from 588,000 to 570,000 per cubic millimeter in two hours, with a return to the preinjection level in six hours.

The fifth control extract was prepared from one half of the spleen of a patient who died of cardiac failure. The specimen, weighing 76 Gm., was obtained ten hours after death and was prepared in the usual manner. The spleen was obtained on Dec. 9, 1937, and the acetone distilled off on December 20. The injection of 20 cc. of this extract into a rabbit on December 27 caused a fall in the platelet count from 587,000 to 540,000 in four hours, with a rise to normal in eight hours.

The sixth control extract was prepared from a spleen removed because of a stab wound. The specimen was obtained at operation on March 5, 1938, and prepared in the routine manner. The acetone was distilled off on March 30. The injection of 20 cc. of this extract into a rabbit on April 12 caused a fall in the platelet count from 640,000 to 610,000 per cubic millimeter in four hours, with a return to the preinjection level in eight hours (chart 5).

COMMENT

Although extracts were made from only three spleens, the results were so uniform that it was felt justifiable to publish these observations before waiting for more material. The three cases were obviously of idiopathic thrombocytopenic purpura.

For the sake primarily of convenience it is suggested that the substance which has thus been found in the extracts of spleens taken from patients suffering from idiopathic thrombocytopenic purpura and which reduces markedly the number of platelets in the circulating blood of a rabbit after intravenous injection be called thrombocytopen, and this new term will therefore be used in the remainder of the article.

Simple as it was, the preparation of the extracts was nevertheless entirely empiric. Previous work in the preparation of intermedin from the hypophysis of cattle [2] showed that the acetone functioned primarily as a preservative and that the active principle was taken out by dilute acetic acid. In the case of the spleen, however, it was acetone that took out the substance that reduced the number of platelets. Whether it is essential to use reagent acetone rather than the commercial variety is open to question. It is probable that the commercial variety will prove to be satisfactory, but only parallel tests can establish this point. Furthermore, whether acetone and not alcohol, ether, water or dilute acetic acid is the best extracting substance remains to be determined.

The correct length of time to allow for the extraction of thrombocytopen by the acetone is still to be established. In the first case this period was sixty-seven days, in the second case one hundred and two days and in the third case six days. The third spleen gave the weakest extract, but it was from a patient who had received roentgen radiation over the splenic area. Thus, radiation brings in another unknown quantity.

Still another factor in the potency of the extracts is the weight of the spleen. Obviously, a large spleen should yield more thrombocytopen than a smaller one. The weight of the three spleens, however, was so nearly the same that the difference in potency of the extracts from the second and third spleens cannot be explained on this basis.

It is possible that thrombocytopen may be found in other organs besides the spleen, and it is thus understandable why the spleen from some patients may not have as heavy a concentration of this substance as the spleen of others and why failures after splenectomy have occurred. The extrasplenic tissue which naturally suggests itself in this connection is the reticulo-endothelial system, for Kaznelson [3] pointed out that the spleen is only a part of the reticulo-endothelial system, and other parts of this system might be primarily affected. Other possible explanations for failures after splenectomy are the presence of accessory spleens (Morrison, Lederer and Fradkin [4]) and the fact that many spleens are removed because of a mistaken diagnosis (Koster [5]).

The theory that the spleen in cases of thrombocytopenic purpura produces a toxin is not a new one. In 1915 Frank [6] advanced the idea that this organ produces a noxious substance that causes thrombopenia by inhibition or destruction of the megakarocytes of the bone marrow. This theory has been the most widely accepted one. Minot [7] in 1917 modified it by suggesting that the deleterious agent can act on the circulating platelets, on the megakaryocytes or on the marrow as a whole. In spite of the relatively long time that this idea of a splenogenous toxin has been current, remarkably few attempts to isolate the toxin have been made. Torrioli and Puddu [8] observed a substance in the spleen of patients with purpura that was toxic to tissue cultures of megakaryocytes. This substance was also seen in other organs and appeared to be related to the presence of reticulo-endothelial tissue in the organs. Attempts have been made more toward understanding purpura itself than toward isolating a cause of idiopathic thrombocytopenic purpura. The work with antiplatelet serum, as begun by Marino [9] in 1905 and Cole [10] in 1907 and more recently carried on by Tocantins,[11] Jones,[12] Lee and Robertson,[13] Watabiki,[14] Bedson [15] and others has greatly advanced the knowledge of purpura itself.

The character of the curve in chart 1 and to a less extent of that in chart 3, showing a sharp fall in the number of platelets and then twenty-four hours later an even sharper rise, brings up the question as to the mode of action of thrombocytopen. More noteworthy

2. Lewis, Dean; Lee, F. C., and Astwood, E. B.: Some Observations on Intermedin, Bull. Johns Hopkins Hosp. **61:** 198 (Sept.) 1937.

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4. Morrison, Maurice; Lederer, Max, and Fradkin, W. Z.: Accessory Spleens: Their Significance in Essential Thrombocytopenic Purpura Hemorrhagica, Am. J. M. Sc. **176:** 672 (Nov.) 1928.

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6. Frank, E.: Die essentielle Thrombopenie: I. Klinisches Bild, Berlin. klin. Wchnschr. **52:** 454, 1915; II. Pathogenese, ibid. **52:** 490, 1915.

7. Minot, G. R.: Diminished Blood Platelets and Marrow Insufficiency: A Classification and Differential Diagnosis of Purpura Haemorrhagica, Aplastic Anemia, and Allied Conditions, Arch. Int. Med. **19:** 1062 (June) 1917.

8. Torrioli, M., and Puddu, V.: Studio sulla biologia di megacariociti sopravviventi in vitro, Policlinico **41:** 245 (May) 1934.

9. Marino, F.: Recherches sur les plaquettes du sang, Compt. rend. Soc. de biol. **58:** 194, 1905.

10. Cole, R. I.: Note on the Production of an Agglutinating Serum for Blood Platelets, Bull. Johns Hopkins Hosp. **18:** 261, 1907.

11. Tocantins, L. M.: Experimental Thrombopenic Purpura in the Dog, Arch. Path. **21:** 69 (Jan.) 1936.

12. Jones, H. W., and Tocantins, L. M.: History of Purpura Haemorrhagica, Ann. M. Hist. **5:** 349 (July) 1933.

13. Lee, R. I., and Robertson, O. H.: The Effect of Antibloodplatelet Serum on Blood Platelets and the Experimental Production of Purpura Haemorrhagica, J. M. Research **33:** 323, 1916.

14. Watabiki, T.: Studies on Experimental Purpura Haemorrhagica Produced by Antibloodplatelet, Kitasato Arch. Exper. Med. **1:** 195, 1917.

15. Bedson, S. P.: Blood Platelet Anti-Serum: Its Specificity and Role in the Experimental Production of Purpura, J. Path. & Bact. **24:** 469 (Oct.) 1921; Experimental Purpura, ibid. **25:** 94 (Jan.) 1922.

than the rapid fall in the number of platelets after the injection is the sudden, sharper return to normal, beginning at the end of twenty-four hours. This sharp rise was invariable and held true for all the experimental animals. The explanation for it may be found in the disappearance of thrombocytopen either because of destruction within the body or from excretion by the animal. It is probable that the substance may be passed out with the urine. Whether thrombocytopen acts directly on the platelets, on their generally accepted precursors, the megakaryocytes, or on bone marrow is yet to be determined.

As regards the chemical nature of thrombocytopen, we can say little at this time except to point out that sometimes a drug like allylisopropylacetylcarbamide, popularly known as sedormid, has been reported as causing a reduction in the number of platelets and producing purpura in some patients.[15a]

One pertinent fact is that no hemorrhagic manifestations were noted in any of the animals in which marked thrombocytopenia had been produced. The possible reasons for this are many. Hemorrhage from the bowel or elsewhere internally might well have occurred and not been noted, as none of the animals were explored. Another probable explanation for the lack of purpura lies in the theory of purpura advanced by Bedson [15] in 1922. He showed by the use of antiplatelet serums that thrombocytopenia alone will not cause purpura. According to his work, there must be some concomitant damage to the capillary walls to produce hemorrhage. These observations were supported by the clinical work of Brill and Rosenthal [16] in 1923. It is therefore entirely possible that the experimental methods used in the work presented here extracted only a substance capable of producing thrombocytopenia. A substance toxic to capillary walls might have been left behind; or, indeed, it may be produced by some other organ. Further work with other methods of extraction might well aid students in reaching some conclusion on this point. Another possible but less probable explanation for the lack of purpura lies in the fact that the critical level of platelets for producing purpura in the rabbit is not known. The platelet levels obtained in this work might not have been low enough, or the low levels might not have been maintained for a sufficient length of time.

SUMMARY

Acetone extracts prepared from the spleen of three patients with idiopathic thrombocytopenic purpura caused a marked reduction in the number of platelets in the circulating blood when injected into laboratory animals. Extracts obtained in identical fashion from control tissue did not furnish this platelet-reducing substance, for which the name thrombocytopen is suggested.

The decrease in the number of platelets in the animal which received an injection was exceeded in promptness only by the sudden and rapid return to normal.

The platelet count could be held at a low level by repeated injections.

Boiling decreased the potency of thrombocytopen.

No evidence of purpura was noted in the experimental animals.

15a. Hoffman, Arthur M.; Kahn, Julius, and Fitzgibbon, J. P.: Thrombocytopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J. A. M. A. **110**: 725 (March 5) 1938. Moody, A. M.: Thrombocytopenic Purpura Following Use of Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), ibid., p. 726.

16. Brill, N. E., and Rosenthal, N.: Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Haemorrhagica), Arch. Int. Med. **32**: 939 (Dec.) 1923; The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Purpura, Am. J. M. Sc. **166**: 503 (Oct.) 1923.

THE USE OF SULFANILAMIDE IN THE DIAGNOSIS AND TREATMENT OF BRUCELLOSIS

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Chemotherapeutic effects of sulfanilamide and its derivatives in certain infectious diseases have been demonstrated in human beings and in experimental animals. Intensive studies have been carried out by Long and Bliss,[1] who in a recent article [2] gave an excellent bibliography of the investigations in this field.

In spite of beneficial effects in some infectious diseases the use of sulfanilamide and its derivatives should be carried out with caution, since an occasional idiosyncrasy toward these drugs does exist.[3] On the other hand, the experimental studies in animals by Marshall and his associates [4] and by Rosenthal [5] indicate that the toxicity of sulfanilamide is small and, as pointed out by Marshall, that the drug is not contraindicated in cases in which definite therapeutic indications exist.

Bliss and Long [6] have noted an increase in phagocytosis and a decrease in free cocci in the peritoneal exudates of mice experimentally infected with beta hemolytic streptococci. It is not possible to say whether the effect of sulfanilamide is primarily on the hemolytic streptococci or on the phagocytes. In experimental Welch bacillus peritonitis in mice, however, Bliss and Long have demonstrated that sulfanilamide inhibited the growth of these organisms in vivo. A bacteriostatic effect with sulfanilamide has previously been shown [6] with Clostridium welchii in vitro. Reasoning by analogy, Long and Bliss feel that the action of sulfanilamide is the same on all susceptible bacteria.

For the past year we have studied the effect of sulfanilamide on the opsonic index in human beings and in animals. The method used for estimating the opsonocytophagic power of the blood is the same as that described for undulant fever by Huddleson.[7] The following degrees of opsonocytophagic activity were recorded for each cell counted: negative, no organisms engulfed; slight, from one to twenty organisms engulfed;

From the Bureau of Laboratories of the Connecticut State Department of Health and the Hartford Hospital.

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3. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, J. A. M. A. **109**: 12 (July 3) 1937. Marshall, E. K., and Walzl, E. M.: Cyanosis from Sulfanilamide, Bull. Johns Hopkins Hosp. **61**: 140 (Aug.) 1937. Menville, J. G., and Archinard, J. J.: Skin Eruptions in Patients Receiving Sulfanilamide, J. A. M. A. **109**: 1008 (Sept. 25) 1937. Newman, B. A., and Sharlit, Herman: Sulfanilamide: A Photosensitizing Agent of the Skin, ibid. **109**: 1036 (Sept. 25) 1937.

4. Marshall, E. K., Jr.; Cutting, W. E., and Emerson, Kendall, Jr.: The Toxicity of Sulfanilamide, J. A. M. A. **110**: 252 (Jan. 22) 1938.

5. Rosenthal, S. M.: Studies in Chemotherapy: II. Chemotherapy of Experimental Pneumococcus Infections, Pub. Health Rep. **52**: 48 (Jan. 8) 1937.

6. Bliss, Eleanor A., and Long, P. H.: Observations on the Mode of Action of Sulfanilamide, J. A. M. A. **109**: 1524 (Nov. 6) 1937.

7. Huddleson, I. F.; Johnson, H. W., and Hammon, E. E.: A Study of the Opsonocytophagic Power of the Blood and Allergic Skin Reaction in Brucella Infection and Immunity in Man, Am. J. Pub. Health **23**: 917 (Sept.) 1933.

moderate, from twenty-one to forty organisms engulfed; marked, over forty organisms engulfed.

In March 1937 we had an opportunity to determine the opsonocytophagic activity of a patient suspected of having brucellosis. A brief history is given:

CASE 1.—J. K., a woman aged 30, complained of generalized muscle pains, chills, fever, nausea and vomiting for two weeks. On physical examination the temperature was 103 F. and the pulse rate 104. The patient was slightly irrational. There were ecchymotic blotches over the extremities and hyperesthesia over the entire body. The course was acutely febrile for three weeks with leukocytosis. Toxic effects on the liver and kidneys were evidenced by bile, albumin three plus and casts in the urine. Agglutination tests for typhoid, paratyphoid and Brucella were negative March 22, 25 and 29. Sulfanilamide, 90 grains (6 Gm.), was given on March 26, 27 and 28 and then stopped. Opsonocytophagic activity on March 30 was 95 per cent marked phagocytosis. Opsonocytophagic activity one week later was 10 per cent marked phagocytosis. Brucella agglutination was found positive April 13. Opsonocytophagic activity April 13 was 58 per cent marked phagocytosis. April 13 the temperature was normal. The patient was released from the hospital April 22. There was no return of symptoms.

In view of Huddleson's classification of susceptible, infected and immune persons on the basis of their opsonocytophagic activity, an index of 95 per cent marked phagocytosis as shown by patient 1 while extremely ill was not expected. The index of 10 per cent marked phagocytosis demonstrated forty-eight hours after sulfanilamide therapy was stopped appeared to be more in line with the patient's condition.

It seemed desirable to determine in other cases of brucellosis the opsonocytophagic activity before and after sulfanilamide therapy. Brief histories of four such cases are given. A marked increase in phagocytic activity occurred following administration of sulfanilamide. Two cases showed an increase of from 8 to 80 per cent marked phagocytosis and from 0 to 92 per cent marked phagocytosis, and two cases showed an increase from 0 to 28 per cent and from 0 to 30 per cent marked phagocytosis. It is of interest to note that of the five cases reported three showed no agglutination with Brucella before sulfanilamide therapy but acquired agglutinins after this drug was administered. A fourth case presented a positive agglutination before the drug was given. In the fifth case no test for agglutinins was made after treatment.

CASE 2.—A. B., aged 33, seen Aug. 18, 1937, had vague complaints for three weeks with high fever and indefinite abdominal pain. On physical examination the temperature was 104.8 F., the pulse rate 92 and the respiratory rate 24. The throat was slightly injected, with no cervical glands; the liver and spleen were slightly palpable. The chest was clear on physical and x-ray examination. Agglutination tests for typhoid and undulant fever were negative. The urine and stools were normal. The Kahn reaction, the blood picture and the Widal reaction were all negative. Treatment consisted of sulfanilamide begun August 18 (90 grains a day for five days, increased to 120 grains [8 Gm.] for five days, then decreased to 60 grains [4 Gm.] for three days). Opsonocytophagic activity August 18 was 47 per cent no phagocytosis, 50 per cent slight, 3 per cent moderate and 0 marked. Following sulfanilamide August 24 opsonocytophagic activity was 8 per cent no phagocytosis, 40 per cent slight, 22 per cent moderate and 30 per cent marked. Typhoid vaccine was given intravenously in three small doses August 20, 21 and 22. The patient's temperature fell to normal September 4 and except for two slight rises has remained normal. September 7 the opsonocytophagic activity was 0 negative, 8 per cent slight, 18 per cent moderate and 74 per cent marked phagocytosis.

CASE 3.—O. M. S., a man aged 55, complained of onset of fever Sept. 13, 1937, rising in one week to 104 F. The agglutination test for undulant fever was negative. The skin test was moderately positive. The opsonocytophagic index showed the patient to be in the infected group: 46 per cent no phagocytosis, 46 per cent slight, 8 per cent moderate, 0 marked. Agglutinations for typhoid and paratyphoid were negative. Physical examination was negative except for fever, low blood pressure and tenderness of the lower part of the legs. Sulfanilamide was started on the eleventh day (120 grains the first week). Opsonocytophagic activity one week after sulfanilamide therapy was started showed 92 per cent marked phagocytosis with 8 per cent moderate. Five days after sulfanilamide was stopped this dropped to 14 per cent marked

TABLE 1.—*Experimental Opsonic Index* *

Guinea Pig	Phagocytosis Before Injection				Phagocytosis Twenty Days After Injection				Phagocytosis Following Sulfanilamide Treatment† Twenty-Three Days After Injection			
	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked
Effect of Sulfanilamide on Guinea Pigs Infected with Brucella Abortus												
148	96	4	0	0	6	32	28	34	0	0	0	100
68	100	0	0	0	6	38	34	22	0	0	10	90
123	96	4	0	0	22	36	25	16	0	0	0	100
202	96	4	0	0	46	18	26	10	0	0	0	100
6	100	0	0	0	6	40	36	18	0	0	4	96
45	94	6	0	0	8	68	16	8	Died before treatment			

	Phagocytosis Before Treatment					Phagocytosis After Treatment†			
	Negative	Slight	Moderate	Marked		Negative	Slight	Moderate	Marked
Effect of Sulfanilamide on Uninfected Guinea Pigs									
209	96	4	0	0	No organisms injected	100	0	0	0
225	96	4	0	0		98	2	0	0
226	100	0	0	0		100	0	0	0
237	92	8	0	0		100	0	0	0

	Phagocytosis Before Injection				Phagocytosis Twenty Days After Injection				Phagocytosis Twenty-Three Days After Injection			
	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked
Untreated Guinea Pigs Infected with Brucella Abortus												
247	92	8	0	0	4	8	40	48	4	0	8	88
266	96	4	0	0	24	30	30	16	24	32	32	12
267	100	0	0	0	4	40	28	28	8	20	32	40
285	92	8	0	0	8	12	20	60	40	32	4	24
388	96	4	0	0	8	40	28	24	16	8	24	52

* Huddleson method.
† Treatment 10 grains over a period of two days (5 grains a day). Index determined forty-eight hours after last injection of drug.

phagocytosis with no phagocytosis in 15 per cent. The agglutination test for Brucella was positive up to 1 : 320 on November 15. The temperature fell to normal on the second day of treatment and has remained there.

CASE 4.—M. S., a woman aged 66, with onset of fever Oct. 20, 1937, complained of drowsiness, fatigue, malaise for the preceding six weeks and afternoon temperature up to 100.6 F. for the past ten days. General physical examination and routine laboratory examinations were negative. The agglutination test for undulant fever was negative, but the cutaneous days, malaise, chills and headache. Physical examination was negative except for the fever. Agglutination and cutaneous tests were both strongly positive June 15. Opsonocytophagic activity June 16 was 12 per cent no phagocytosis, 38 per cent slight, 44 per cent moderate and 6 per cent marked. Sulfanilamide was started (June 18) (only 60 grains was given). Therapeutic brucellin 0.1 mg. intracutaneously June 19 gave a severe reaction and was stopped. Opsonocytophagic activity June 22 was 20 per cent moderate and 80 per cent marked phagocytosis. Opsonocytophagic activity June 25 was 11 per cent no phago-

TABLE 2.—*Further Experiments on Opsonic Index* *

	Phagocytosis Before Injection				Phagocytosis Ten Days After Injection				Phagocytosis Following Sulfanilamide Treatment† Thirteen Days After Injection			
Guinea Pig	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked
Effect of Sulfanilamide on Guinea Pigs Infected with Brucella Abortus												
152	100	0	0	0	100	0	0	0	0	0	0	100
156	100	0	0	0	68	20	8	4	0	4	0	96
159	100	0	0	0	40	28	12	20	0	0	5	95
160	100	0	0	0	64	32	0	4	0	0	0	100
162	100	0	0	0	100	0	0	0	0	0	0	100
369	100	0	0	0	100	0	0	0	0	0	0	100
358	100	0	0	0	36	56	8	0	0	8	0	92
189	100	0	0	0	100	0	0	0	0	0	0	100
383	100	0	0	0	84	16	0	0	0	0	0	100
392	100	0	0	0	16	64	12	8	0	0	0	100
Effect of Sulfanilamide on Uninfected Guinea Pigs												
	Phagocytosis Before Treatment								Phagocytosis After Treatment			
	Negative	Slight	Moderate	Marked					Negative	Slight	Moderate	Marked
341	100	0	0	0	No organisms injected				100	0	0	0
356	100	0	0	0					100	0	0	0
363	100	0	0	0					100	0	0	0
274	100	0	0	0					100	0	0	0
Untreated Guinea Pigs Infected with Brucella Abortus												
	Phagocytosis Before Injection				Phagocytosis Ten Days After Injection				Phagocytosis Thirteen Days After Injection			
	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked	Negative	Slight	Moderate	Marked
157	96	4	0	0	56	44	0	0	Died			
161	100	0	0	0	8	72	12	8	Died			
347	100	0	0	0	20	40	20	20	Died			
359	100	0	0	0	72	28	0	0	20	36	8	36
360	100	0	0	0	100	0	0	0	Died			
376	100	0	0	0	8	8	40	44	Died			
402	100	0	0	0	8	20	44	28	12	8	36	44

* Huddleson method.
† Treatment 10 grains over a period of two days (5 grains a day). Index determined forty-eight hours after last injection of drug.

TABLE 3.—*Effect of Serums and Cells of Infected, Treated Guinea Pigs on Heterologous Cells and Serums*

Serum of Infected Treated Guinea Pigs	Cells of Normal Guinea Pigs: Marked Phagocytosis				Cells of Uninfected Treated Guinea Pigs: Marked Phagocytosis				Cells of Infected Treated Guinea Pigs	Serum of Normal Guinea Pigs: Marked Phagocytosis				Serum of Uninfected Treated Guinea Pigs: Marked Phagocytosis			
	301	312	318	319	209	225	226	237		301	312	318	319	209	225	226	237
148	100%	100%	100%	100%	100%	100%	100%	100%	148	0	0	0	0	0	0	0	0
68	100%	100%	100%	100%	100%	100%	100%	100%	68	0	0	0	0*	0	0	0	0
123	100%	100%	100%	100%	100%	100%	100%	100%	123	0	0	0	0	0	0	0	0
202	100%	60%	100%	100%	100%	96%	100%	94%	202	0	0	0	0	0	0	0	0
6	100%	100%	100%	100%	100%	100%	100%	100%	6	0	0	0	0*	0	0	0	0

* In these two counts 4 per cent of the cells showed moderate phagocytosis, but in no other instance was more than slight engulfment shown.

test was strongly positive. Opsonocytophagic activity November 5 was 100 per cent no phagocytosis. After an irregular fever for three weeks the patient was given sulfanilamide (300 grains in one week). Opsonocytophagic activity then showed 28 per cent marked and only 2 per cent no phagocytosis. The temperature, which had been normal after the first day of sulfanilamide, returned and another course of sulfanilamide was given (100 grains [6.5 Gm.] a day for five days). The opsonocytophagic activity was then found to be 28 per cent marked and 0 no phagocytosis. A second agglutination test was positive up to 1 : 160. The patient had fever altogether for approximately forty days with remissions during sulfanilamide therapy. She was given a fotal of 300 grains (20 Gm.) during the first course and 500 grains (32 Gm.) during the second. There has been no return of symptoms.

CASE 5.—F. B., a farmer aged 54, seen June 14, 1937, had many cows that had aborted. He complained of fever for nine cytosis, 29 per cent slight, 40 per cent moderate and 20 per cent marked phagocytosis. The patient was discharged June 26 with a normal temperature.

To determine whether sulfanilamide therapy in other infections stimulates an increase in opsonocytophagic activity toward Brucella, five patients with gonorrhea and one patient with relapsing fever were each given a total of 300 grains (20 Gm.) of sulfanilamide over a period of five days. The opsonocytophagic activity was determined before and after administration of the drug. No appreciable change occurred in the opsonocytophagic activity toward Brucella after sulfanilamide therapy.

In the control gonorrhea group the opsonic activity of the blood of these patients was also tested against Neisseria gonorrhoeae, Monilia candida, staphylococci, Eberthella typhosa, Escherichia coli, pneumococci types

I, III and VIII and, in some instances, beta hemolytic streptococci. A definite increase in opsonic activity was demonstrated for both hemolytic streptococci and staphylococci but no appreciable change could be shown with any of the other organisms listed.

ANIMAL EXPERIMENTS

Eleven guinea pigs were injected each with 100 million live Brucella abortus organisms suspended in

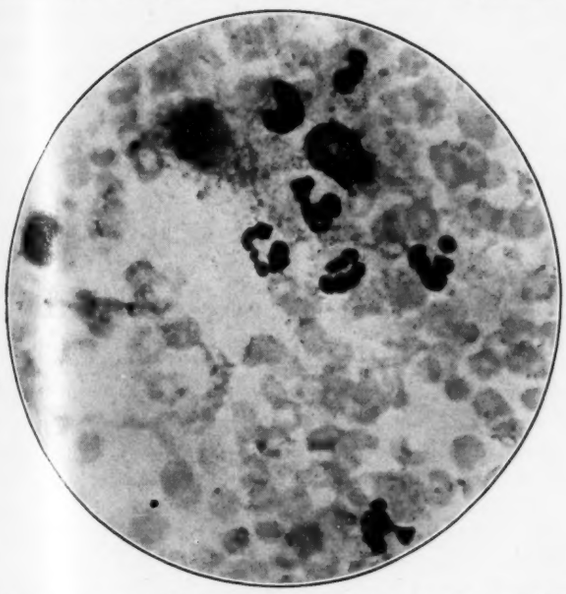

Fig. 1 (guinea pig 162).—Opsonocytophagic index before sulfanilamide treatment.

saline solution. On the twentieth day after injection an opsonocytophagic index was determined on each animal and on four normal controls. Six of the infected guinea pigs and the four normal guinea pigs were then injected subcutaneously with 5 grains (0.3 Gm.) of sulfanilamide suspended in olive oil. Twenty-four hours later a similar injection was made (total 10 grains [0.6 Gm.]). Forty-eight hours after the last injection of sulfanilamide opsonocytophagic tests were made on all guinea pigs comprising five [8] infected treated, four uninfected treated and five infected untreated. The results are given in table 1.

All the infected animals treated with sulfanilamide showed marked increases in phagocytic activity. The average percentage of cells showing marked phagocytosis before treatment was 20 per cent and after treatment 97 per cent.

In the infected untreated group of animals the average percentage of cells showing marked phagocytosis on the twentieth day after injection was 35 and on the twenty-third day only 43. The uninfected treated guinea pigs showed no change in phagocytic activity.

An average increase in opsonic activity from 20 to 97 per cent of marked phagocytosis in Brucella infected guinea pigs following treatment with sulfanilamide is a significant one. It was felt, however, that an even greater difference might be demonstrated if sulfanilamide therapy was started earlier in the process of infection.

A series of seventeen guinea pigs was injected intraperitoneally with Brucella abortus in a dose of 100 million. Ten days after injection an opsonic index for Brucella was done on each animal and 5 grains of sulfanilamide in olive oil was injected subcutaneously into ten of the infected guinea pigs, seven being withheld as untreated controls. Four normal guinea pigs were each given 5 grains of sulfanilamide at the same time the infected animals were treated. On the following day a further dose of 5 grains of sulfanilamide in olive oil was injected subcutaneously into both the infected and the uninfected group. Forty-eight hours later a second opsonic index was determined on all guinea pigs. The results obtained are shown in table 2.

The change in the degree of phagocytosis in infected guinea pigs following treatment with sulfanilamide was even greater than in the first series (table 1). Four guinea pigs in the infected treated group (152, 162, 309 and 189, table 2) which had shown 100 per cent negative phagocytosis before treatment with sulfanilamide showed 100 per cent marked phagocytosis after treatment.

Figures 1 and 2 are reproductions of photomicrographs of typical fields observed (guinea pig 162) before and after treatment with sulfanilamide. Figure 3 shows the opsonocytophagic activity of the blood of guinea pig 309 after treatment with sulfanilamide. Before sulfanilamide treatment the leukocytes show no engulfment and the Brucella organisms are evenly distributed throughout the field. After treatment not only is there marked engulfment but there appears to be a positive chemotaxis of the organisms for the white cells. This phenomenon has been noted throughout these studies with Brucella organisms.

Five guinea pigs in the control (infected untreated) group died between the tenth and the thirteenth day of the experiment (table 2). In the treated uninfected group no change in opsonic index was observed.

In order to determine whether sulfanilamide was present in the blood of infected guinea pigs at the

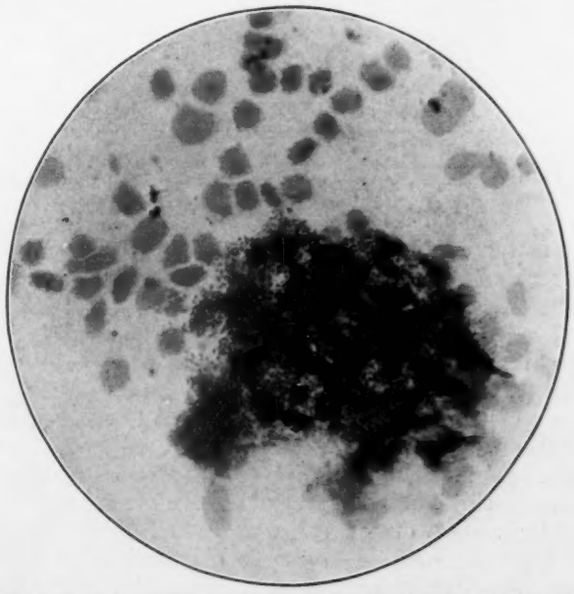

Fig. 2 (guinea pig 162).—Opsonocytophagic index after sulfanilamide treatment.

time that marked phagocytic activity was demonstrated, the blood serums of all treated animals were tested for sulfanilamide. In the first group tested (table 1) none of the infected treated animals showed sulfanilamide in their blood serum, while those which were not infected but treated simultaneously with the same amount of sulfanilamide as the test group all showed

8. One infected animal in this group died before treatment.

some sulfanilamide present. In the second series the results were not as uniform although of the ten infected treated animals seven showed no sulfanilamide in their blood while in the control group of four animals two showed sulfanilamide in the blood.

Since serums from the first group of guinea pigs (table 1) showed no sulfanilamide and the blood of these animals was extremely active against Brucella organisms, it seemed advisable to determine whether the cells or the serum of such infected treated animals was the active agent in bringing about marked phagocytosis. Accordingly, in all five guinea pigs of the infected treated group (table 1) blood was withdrawn from the heart into citrate solution (final concentration 0.78 per cent) and the serum removed by centrifugation. The cells were washed twice with salt solution (0.85 per cent).

Opsonocytophagic tests were then done after serums of infected treated guinea pigs were combined with the cells of normal guinea pigs and with the cells of uninfected treated guinea pigs. Tests were also made

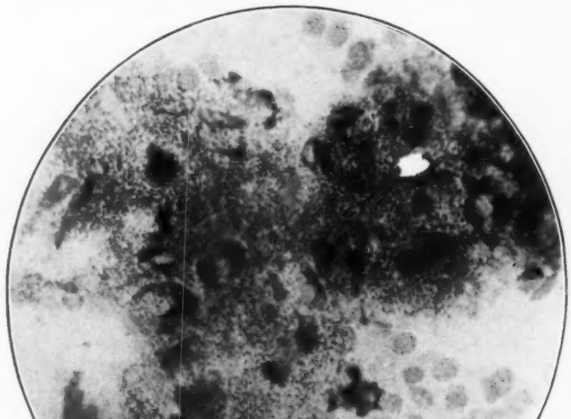

Fig. 3 (guinea pig 309).—Opsonocytophagic index after sulfanilamide treatment.

with the cells of the infected treated guinea pigs suspended in the serums of normal guinea pigs and with these cells in the serums of uninfected treated guinea pigs. In each case 0.1 cc. of cells, 0.1 cc. of serum and 0.1 cc. of a Brucella abortus suspension were mixed in agglutination tubes and incubated in the water bath at 37 C. for one-half hour. Blood smears were made in the usual way and stained with Hastings' stain and the degrees of phagocytic activity determined. The results obtained are given in table 3.

The serum of an infected treated guinea pig is capable of stimulating the cells of both normal guinea pigs and of treated uninfected guinea pigs to the same degree of phagocytosis that it stimulated its homologous cells. When normal human cells were suspended in serums of infected treated guinea pigs a similar stimulation of phagocytosis occurred. On the other hand the cells of infected treated pigs in the presence of normal serum or serum from treated uninfected guinea pigs completely lost their phagocytic activity.

An attempt was made to sensitize cultures of Brucella by treatment with sulfanilamide in vitro. Cultures so treated were not engulfed by either normal human or normal guinea pig cells. Conversely, treatment of normal guinea pig or normal human blood in vitro failed to increase opsonic activity against untreated Brucella or against Brucella treated as described.

These results show that the activity evidenced in the serums of sulfanilamide-treated infected guinea pigs, but not in the leukocytes, is not the result of the presence of free sulfanilamide. These studies, however, suggest that the activity results in a stimulation of opsonins as the direct or indirect effect of the treatment on the infected animal.

To determine the specificity of the active agent, the blood of guinea pigs infected with Brucella and of patients with brucellosis has been tested against other organisms. Guinea pigs infected with Brucella and treated with sulfanilamide show a marked increase in opsonic activity for Brucella, but only slight changes in opsonocytophagic power could be demonstrated for Shigella paradysenteriae Sonne and Harris, Shigella alkalescens and Eberthella typhosa.

The blood of patients with brucellosis, although showing marked opsonocytophagic activity against Brucella following sulfanilamide therapy, showed no appreciable change in opsonic activity against E. typhosa, Salmonella schottmülleri, Shigella alkalescens, Monilia, Salmonella suipestifer or Escherichia coli. However, a marked increase in phagocytic activity was shown with hemolytic streptococci and staphylococci.

It should be stressed that both normal persons and normal guinea pigs treated with sulfanilamide show no increase in their opsonocytophagic activity for Brucella or for any of the other organisms tested, with the exception of the activity in human beings for hemolytic streptococci and staphylococci.

COMMENT

It has been estimated that from 5 to 15 per cent of true cases of undulant fever fail to show agglutinins. In our experience the intracutaneous test may be positive in uninfected persons and the opsonocytophagic test may show a positive result in uninfected persons and, vice versa, absence of phagocytic activity in infected persons.

The investigations by Baumgartner, Robinson and Evans [9] of the opsonocytophagic test as a means of determining Brucella infection indicate that it may be difficult to interpret even when both the cutaneous reaction and results of agglutination are known. Our studies indicate that in persons infected with Brucella the use of sulfanilamide therapy markedly stimulates the phagocytic activity of the white blood cells for Brucella. Since sulfanilamide-treated normal persons and persons with other infections show no change in opsonocytophagic activity for Brucella organisms, it appears that the use of this drug in suspected cases of brucellosis should be a helpful diagnostic procedure. The results obtained in infected sulfanilamide-treated guinea pigs were similar to those demonstrated in human beings. Berger and Schnetz [10] recently reported the successful treatment in a case of undulant fever with prontosil. Our results in a series of five cases of brucellosis indicate that sulfanilamide may be a valuable therapeutic aid in the treatment of this disease.

9. Baumgartner, L.; Robinson, F., and Evans, A.: An Evaluation of the Opsonocytophagic Activity Test in the Diagnosis of Brucella Infections, reported at the American Public Health Association Meeting in New York in October 1937.

10. Berger, W., and Schnetz, H.: Success of Treatment with Prontosil in a Case of Bang's Disease, Med. Klin. **33**: 594 (April 30) 1937.

The investigations of Long and Bliss indicate that sulfanilamide acts in vivo by bringing about a change in the susceptible micro-organisms which permits phagocytosis. In a recent article Osgood and Brownlee [11] note that the major action of sulfanilamide on beta hemolytic streptococci seems to be neutralization of the toxins and that the drug has no direct effect on phagocytosis. The latter authors used in vitro experiments with cultures of human marrow to support their contentions, whereas Long and Bliss came to their conclusions following in vivo experiments in mice.

Our studies show that in cases of human brucellosis and in guinea pigs infected with Brucella abortus, treatment with sulfanilamide markedly increases phagocytosis. Individuals infected with other diseases and normal guinea pigs treated with sulfanilamide show no change in their opsonocytophagic activity for Brucella abortus. Further, the blood of normal human beings or normal guinea pigs, even when treated in vitro with sulfanilamide, shows no change in opsonocytophagic activity when mixed with untreated Brucella abortus or with sulfanilamide-treated organisms.

It has been possible in infected guinea pigs treated with sulfanilamide to demonstrate absence of the drug in the blood at the time at which marked phagocytosis occurs and, further, to transfer this marked phagocytic activity to normal guinea pig and human cells by suspending them in the serum of infected treated guinea pigs. Since the presence of sulfanilamide as such is not essential for the demonstration of marked phagocytosis in infected treated guinea pigs, it would appear that the effect of the drug is an indirect one. Osgood and Brownlee's demonstration of destruction of the erythrotoxin of beta hemolytic streptococci with sulfanilamide would indicate that at least with this organism one of the mechanisms of its action is the destruction of such exotoxins. On the other hand, with Brucella abortus, which produces no exotoxin, some other explanation for the action of the drug on this organism is necessary. It is well known that Brucella filtrates are extremely toxic and produce in infected and sensitized individuals marked reaction when injected intracutaneously in small amounts. The toxicity of such filtrates are manifested not only by local reactions but also by definite systemic reactions such as malaise, high fever and headache. It appears to us that sulfanilamide acts indirectly in Brucella infections by increasing the opsonic power of the blood and thus neutralizing the effect of the endotoxin or aggressin-like substances produced by this organism allowing phagocytosis to take place. The fact that it was not possible to stimulate the opsonic power of the blood toward Brucella of uninfected human beings or guinea pigs by treatment with sulfanilamide would indicate that an infective or immunizing process must be in progress for the drug to stimulate phagocytosis in this disease. However, an active infective process with beta hemolytic streptococci or staphylococci does not appear to be necessary for the drug to stimulate phagocytosis of these organisms. In normal or in infected human beings treated with sulfanilamide the opsonocytophagic power of the blood was increased markedly for the latter organisms. An explanation of the phagocytic activity induced by sulfanilamide therapy in human beings against beta hemolytic streptococci and staphylococci may lie in the wide distribution of these organisms with correspondingly increased chances for previous infection or for partial immunization by subinfective doses. Experimental studies of this phase of the problem in animals are now in progress.

11. Osgood, E. E., and Brownlee, Inez E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110:** 349 (Jan. 29) 1938.

CONCLUSIONS

The use of sulfanilamide would appear to be a valuable aid in the diagnosis and treatment of human brucellosis.

Animal experimentation indicates that in Brucella infections sulfanilamide markedly increases opsonocytophagic activity for Brucella organisms.

In Brucella infections sulfanilamide appears to act through stimulation of the defense mechanism of infected animals by increasing the production of specific opsonins, thus affecting neutralization of the endotoxic or aggressin-like substances produced by these organisms, with resulting phagocytosis.

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THE LATERAL PYELOGRAM AS A DIAGNOSTIC AID IN PERINEPHRIC ABSCESS

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Perinephric abscess is an age old condition recognized as a clinical entity for many years, yet it remains undiagnosed in a large percentage of cases. In diagnosis this condition may be confused with traumatic rupture of the kidney, pyonephrosis, nephrolithiasis, renal or perirenal tumors, lumbar arthritis, lumbar hernia, retrocecal appendicitis, subdiaphragmatic abscess, gallbladder disease, tuberculosis of the spine or hip, osteomyelitis of the ribs or a ruptured viscus. Consequently, any patient with a history of chills, fever or lumbar pain and presenting tenderness of the costomuscular angle, leukocytosis and rigidity of the lumbar and psoas muscles should undergo a complete urologic examination.

In 1921 Bela Alexander [1] of Leipzig reported two cases of perinephric abscess showing a disappearance of the psoas line and a poorly defined kidney outline on the affected side; in one of the cases there was a curvature of the spine and a retraction of the thigh. In 1928 Beer [2] and Lipsett [3] independently and simultaneously brought out and stressed these signs in the diagnosis of perinephric abscess. In 1929 Peacock [4] stressed the fact that a retrorenal or a retroperitoneal mass producing an anterior and a lateral displacement of the kidney and ureter could be demonstrated by stereoscopic roentgenograms. In his opinion, lateral roentgenograms would show the same displacement, but such a procedure offered too many difficulties. In 1934 Mertz and Hamer [5] demonstrated the value of lateral pyelograms in urologic diagnosis, but in their series they made no mention of nor did they demon-

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1. Alexander, Bela, quoted by Peacock.[4]
2. Beer, Edwin: Roentgenographic Evidence of Perinephric Abscess, J. A. M. A. **90:** 1375 (April 28) 1928.
3. Lipsett, P. J.: Roentgen Ray Observations in Acute Perinephric Abscess, J. A. M. A. **90:** 1374 (April 28) 1928.
4. Peacock, A. H.: Perinephritic Abscess, Surg., Gynec. & Obst. **47:** 757-765 (June) 1929.
5. Mertz, H. O., and Hamer, H. G.: The Lateral Pyelogram: An Investigation of Its Value in Urologic Diagnosis, J. Urol. **31:** 23-54 (Jan.) 1934.

strate a perinephric abscess. Cabot[6] stresses the importance of the limitation of movement of the inner portion of the diaphragm in large perinephric abscesses.

Failure to recognize the condition or to institute proper and early treatment is probably the explanation of the high mortality rates reported in the literature; therefore, any diagnostic procedure which facilitates an accurate diagnosis will help to lower these rates.

REPORT OF CASES

In four cases in which perinephric abscess was clinically suspected lateral pyelograms were made, and in the advanced cases the corresponding kidney and ureter were found to be markedly displaced anteriorly. Although lateral pyelograms have been used elsewhere in the diagnosis of various renal and retroperitoneal lesions, I[7] am unable to find any reference of this procedure being used in perinephric abscess except in my preliminary report in 1937.

CASE 1.—A white youth aged 19 suffered from pain in the left lumbar region and from occasional chills and fever for fourteen months. Furuncles about the face appeared shortly after the onset of pain. Examination revealed that the patient was emaciated, with a limping gait, a slight curvature of the spine and a tendency to elevate the left thigh. There was pain on extension of the left thigh, rigidity of the left lumbar muscles, a deep-seated, firm, slightly tender mass in the region of the left kidney, a mild leukocytosis and a temperature of 99 F. The blood chemistry, the urine from the bladder and from each kidney, and the function of each kidney were normal.

A roentgenogram of the kidneys, ureters and bladder showed a curvature of the lumbar spine, with the concavity pointing to the left side and an obliteration of the shadow of the left psoas muscle. A left retrograde pyelogram, with anteroposterior and lateral views, showed an enlarged kidney with a compression of the upper calix and a marked anterior displacement of the kidney and ureter (fig. 1). Oct. 29, 1936, a left-sided perinephric

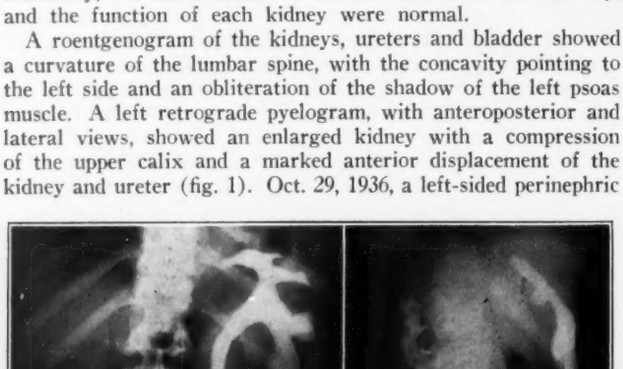

Fig. 1 (case 1).—*A*, a preoperative retrograde pyelogram of a patient with a perinephric abscess, showing the enlarged left kidney, with a slight blunting of the lower calices and a compression of the upper calix. The spine shows a curvature, with the concavity to the left side. *B*, a lateral pyelogram presenting a marked anterior displacement of the kidney and an elongated, regular, smooth, arclike displacement of the ureter.

abscess of Staphylococcus albus origin, containing approximately 1,500 cc. of thick purulent material, was drained. Four months after operation the patient returned for an examination at my request. A retrograde pyelogram with anteroposterior and lateral views showed the pelvis and calices to be normal and the kidney and ureter to be in normal positions (fig. 2).

CASE 2.—A white man aged 27 suffered from pain in the right lumbar region and from chills and high fever for four months. There was a loss of 15 pounds (6.8 Kg.) and a limping gait, increased frequency and nocturia. On examination the patient was weak and emaciated and had a temperature of 103 F., tenderness over both lumbar regions, a tender movable mass in the

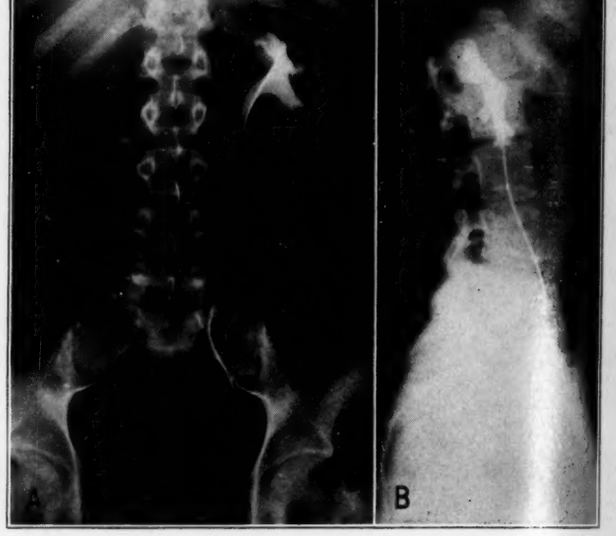

Fig. 2 (case 1).—*A*, a retrograde pyelogram made four months after operation, showing the pelvis and calices to have returned to their normal size and shape. The spine has also returned to a normal straight line. (Compare with figure 1 *A*.) *B*, a lateral pyelogram made four months after operation, showing the kidney and ureter to be in normal position. (Compare with figure 1 *B*.)

right side, rigidity of the muscles of the right lumbar region and a slight flexion of the right thigh. A roentgenogram of the abdomen revealed a slight curvature of the lumbar spine, with the concavity pointing to the right side and an obliteration of the shadow of the right psoas muscle. A right-sided retrograde pyelogram revealed an overdistended pelvis with some pyelovenous backflow. A lateral view showed the kidney and ureter to be displaced anteriorly in a smooth, arclike manner.

April 12, 1937, a large right-sided perinephric abscess was drained. Twenty-one days later a right-sided retrograde pyelogram in the anteroposterior and lateral views revealed the kidney to be of normal size and in a normal position.

CASE 3.—A white man aged 33 suffered from cramping pains in the right side of the abdomen for seven days and in the right kidney for two days. A year previously an appendical abscess had been drained. Examination revealed spasticity of the right lumbar muscles with tenderness in that region and pain on extension of the right thigh. The urine was essentially normal. A leukocyte count of 12,350 was found. The urine specimen from each kidney as well as the function of each kidney was normal. A roentgenogram of the abdomen was obscured by gas shadows. Retrograde pyelograms in the anteroposterior position revealed an enlarged left kidney, low in position, and a right kidney with an incomplete filling of the lower calix. A lateral view showed the right kidney and ureter to be displaced anteriorly in a smooth, regular, arclike manner.

April 12, 1937, a large right-sided perinephric abscess of Bacillus coli origin was drained. Seventeen days later a right retrograde lateral pyelogram showed the kidney to be in a normal position, but the lower end of the ureter was still somewhat displaced anteriorly. This deformity was probably due to adhesions from the old appendical abscess.

CASE 4.—A white boy aged 4 years suffered from nausea and vomiting six days prior to admission. Following a purgative, pain developed in the lower right quadrant radiating to the right thigh and to the costal margins posteriorly. Examination revealed that the child was moderately ill, with a temperature

6. Cabot, Hugh: Blood Stream Infection of the Kidney, Brit. J. Urol. **8**: 233 (Sept.) 1936; Review of the Sixth Congress of the International Society of Urologists, Surg. **1**: 147 (Jan.) 1937.

7. Menville, J. G.: Lateral Pyelogram as an Aid in the Diagnosis of Perinephritic Abscess: Preliminary Report, New Orleans M. & S. J. **90**: 37 (July) 1937.

of 102 F., a marked tenderness in the right lumbar region and in the abdomen to the right of the umbilicus. The urine from the bladder and from each kidney was normal. Retrograde pyelograms revealed that the pelves and calices were normal. A lateral view of the right pyelogram showed that the kidney and ureter were displaced only slightly anteriorly and had no arclike curves. June 10, 1937, the kidney was explored and the lower pole was found to be inflamed, indurated and adhering to the retroperitoneum. About 3 cc. of purulent material was drained from the wound. A generalized peritonitis developed and the patient died eleven days after operation.

COMMENT

In the first case presented in this paper a lateral pyelogram was attempted in an effort to verify the diagnosis of perinephric abscess. The technic of having the patient lie on the affected side, perpendicular to the x-ray film, while the pyelogram was made, was so simple and so successful that the same procedure was carried out in the subsequent cases. However, the accuracy of a lateral pyelogram is dependent on the patient's lying perpendicular to the film, for if the side of the patient away from the film is tilted back the kidney nearest the film will normally cast a shadow anterior to the vertebral column.

The anterior displacement of the kidney and ureter in a smooth, regular, elongated arclike manner in patients with a large perinephric abscess is produced by the retroperitoneal accumulation of purulent material. A similar displacement by other forms of fluid is possible; I have seen such a condition following the extravasation of urine from a traumatic rupture of the kidney. Blood and chyle should act in a similar manner. In the absence of free fluid in the retroperitoneal space, I know of no condition that will produce a smooth anterior arclike deformity of the kidney and ureter with the exception of an aneurysm of the abdominal aorta.

In early cases of perinephric abscess in which only a few cubic centimeters of purulent material has accumulated, the displacement of the kidney and ureter may be so slight as to be scarcely noticeable. However, if there is sufficient infection to produce edema of the surrounding tissue, the kidney and possibly the ureter will be displaced anteriorly but not in an arclike fashion. The lateral pyelogram produces a typical deformity in advanced cases of perinephric abscess, while in the early cases the displacement is slight. Any displacement of the kidney anteriorly is suggestive of retroperitoneal disorder.

CONCLUSION

Lateral pyelograms in three cases of perinephric abscess presented a uniform, anterior, arclike displacement of the kidney and ureter on the affected side. Postoperative lateral pyelograms in the same cases showed the kidneys and ureters to be in normal positions with no evidence of anterior displacement. A lateral pyelogram in a very early case of perinephric abscess showed a minute anterior displacement of the kidney and ureter.

Maison Blanche Building.

Soil as Important as Seed.—But today we can recognize that bacteriology has not brought us all the gifts we anticipated. For it overlooked for a time that the soil was an important factor in infection as well as the seed. There is not only the microbe which invades the individual but there is the reaction of that individual to the microbe to be considered.—Langdon-Brown, Walter: The Dead Hand in Medical Science, *Lancet* **1**:278 (Jan. 29) 1938.

FIBROUS AND FATTY REPLACEMENT OF RENAL PARENCHYMA

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Replacement of renal parenchyma by fatty tissue has been until recently regarded as a rare condition, as a specific type of process resulting from infection and as limited almost entirely to the so-called surgical diseases of the kidney. Mention of this disease in the literature has been infrequent, and the confusion as to its cause is indicated by the profusion of titles given it. These include fatty transformation of the kidney, fatty degeneration of the kidney, lipomatosis renis, substitutio renis adiposa, lipomatous paranephritis, lipomatous nephritis, lipome intranephritic and degeneration lipoma. The main purpose of this paper is at once to clarify, simplify and enlarge the concept of this particular entity.

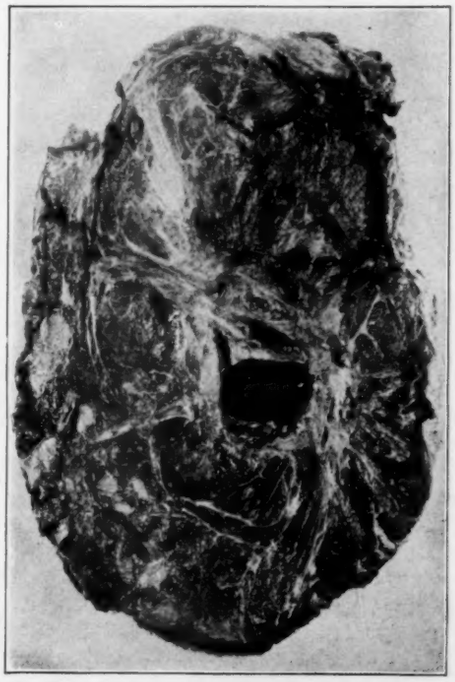

Fig. 1 (case 1).—Nephrolithiasis, grade 4 replacement; sudan IV.

In the early literature replacement lipomatosis was at times confused with true lipoma of the kidney, a condition which is quite rare. Elansky [1] quoted Lubarsch as saying that in 40,000 autopsies only one lipoma was observed in the kidney. Moreover, a true lipoma of the kidney is usually small, encapsulated, located directly beneath the capsule of the kidney and surrounded by normal renal tissue. Replacement lipomatosis is not found in a normal kidney, being an invasive proliferation of fat extending from the hilus and the pelvis toward the periphery of the kidney as a replacement process supplanting destroyed or atrophied parenchyma.

From the Departments of Urology and Pathology of St. Francis Hospital and the Ohio State University College of Medicine.
Dr. W. N. Taylor, head of the Department of Urology of the Ohio State University College of Medicine, allowed us to include two of his cases in this report.

1. Elansky, N. N.: Lipomatosis Perirenalis cum Atrophia et Substitutione Adiposa Renis, Ztschr. f. urol. Chir. **26**: 431-446, 1929.

There are at present two main theories as to the cause and the nature of this fatty replacement of renal parenchyma: 1. Chronic inflammatory processes in the kidney stimulate hyperplasia of the perirenal and peripelvic fat, which then enter the kidney through the capsule or hilus by active invasion, producing atrophy of renal parenchyma. Von Rokitansky,[2] Israel[3] and Matsuoka[4] advocate this theory. 2. Atrophy of the kidney due to some destructive process is the primary factor and is followed by secondary invasion on the part of the proliferating fat. The majority of investigators, including Borst,[5] Gimpelson,[6] Elansky,[1] Bacon and LeCount,[7] Kutzmann[8] and Krymholz,[9] favor this theory, whereas a minority hold to the first hypothesis.

In regard to these varying concepts of the cause, it is noteworthy that the kidney retains its integrity despite pressure brought to bear by a retroperitoneal tumor or other large intra-abdominal mass. This fact does not tend to substantiate the theory of atrophy produced by pressure from proliferation of fat. It has been agreed by practically all investigators up to this time that the condition as a whole is due to some slow inflammatory process. Kutzmann[8] has stated that calculous disease is the primary and initial factor, which leads to infection and destruction of kidney tissue with resulting pyonephrosis. Borst[5] expressed the opinion that a proliferation of fatty tissue, such as compensates for the defect produced by muscular atrophy in certain types of muscular dystrophy, is active here also. Gimpelson[6] stated that this phenomenon belongs to the classification hyperplasia ex vacuo: substitution of fat for destroyed parenchyma. This process can be considered biologically as an attempt of the organism to maintain its equilibrium.

Fig. 2 (case 2).—Nephrolithiasis, grade 3 replacement; no stain.

Baader[10] in 1778 first reported the condition in which ureteral calculus, pyelonephritis and fatty changes are observed at autopsy; but it was not until 1837 that Rayer[11] described in detail a case of renal lipomatosis. Previous to 1900 the condition had been seen only at autopsy; Israel[3] in 1901 was the first to report it postoperatively. In 1931 an excellent review of the literature was made by Kutzmann,[8] who collected thirty-two cases and added one of his own. Of these thirty-two cases, twenty-eight were reported from foreign sources. Since 1931 eighteen additional cases have been recorded in the American literature: eleven by Young,[12] two by Culver[13] and one each by White and Cambridge,[14] Exley and Devereaux,[15] Kretschmer and Pierson,[16] Peacock and Balle[17] and Wethall. Krymholz in 1932 added two cases of his own to twelve cases which he collected, two of which had been mentioned previously by Kutzmann; he also reported that Tjurkoff had collected seven cases, two of which also were mentioned by Kutzmann. Since the report of Krymholz one case each has been recorded by Scandurra[18] and Gridnev,[19] making a total of seventy reported cases.

Fig. 3 (case 3).—Nephrolithiasis, grade 3 replacement; sudan IV.

Kutzmann reported that stone was found in 79 per cent of his collected cases. In the total seventy reported cases the frequency of stone was 76 per cent. Lipomatosis usually occurs unilaterally, favoring neither the right nor the left kidney, though Richards[20] and Griffon[21] reported cases of bilateral involvement. The age of the patient varied from 10 years, in Browne's[22] case, to 77, the age of Peacock and Balle's[17] patient, a man. The period of greatest incidence is between the ages of 45 and 60 years. The frequency is the same in the two sexes.

In the reported cases the clinical diagnosis was made variously as calculous pyonephrosis with perinephritis, calculous pyonephrosis, tumor of the kidney and tuberculosis of the kidney. Krymholz[9] was the first to report two cases of renal tuberculosis accompanied by lipomatosis. No case has been reported in which the diagnosis was made preoperatively.

2. von Rokitansky, Carl: Handbuch der pathologischen Anatomie Vienna, Braumüller & Seidel **3:** 336, 1855.
3. Israel, James: Chirurgische Klinik der Neirenkrankheiten, Berlin, A. Hirschwald, 1901.
4. Matsuoka, Y.: Contributions to the Pathology of Lipomatosis, J. Path. & Bact. **20:** 111-112, 1915.
5. Borst, Max: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, p. 143.
6. Gimpelson, E.: Zu Frage der Fettsubstitution der Nieren, Ztschr. f. urol. Chir. **26:** 651-658, 1929.
7. Bacon, L. H., and LeCount, E. R.: Fat Replacement of the Kidney in Chronic Suppurative Pyelitis, Tr. Chicago Path. Soc. **13:** 23, 1928.
8. Kutzmann, A. A.: Replacement Lipomatosis of the Kidney, Surg., Gynec. & Obst. **52:** 690 (March) 1931.
9. Krymholz, M.: Fat Substitution of Atrophic Kidney, Ztschr. f. urol. Chir. **36:** 343-360, 1933.
10. Baader, cited by La Crampe-Loustan, C.: Essai sur l'adipose du rein, Thèse de Paris, 1881.
11. Rayer, P. F. O.: Traité des maladies des reins, Paris, J. B. Baillière, 1839.
12. Young, H. H.: Lipomatosis or Destructive Fat Replacement of the Renal Cortex, J. Urol. **29:** 631-644 (June) 1933.
13. Culver, Harry: Replacement Lipomatosis of Kidney, S. Clin. North America **14:** 813-819, 1934.
14. White, E. W., and Cambridge, H. S.: Lipomatosis of the Kidney with Report of a Case, J. Urol. **31:** 699-710 (May) 1934.
15. Exley, E. W., and Devereaux, T. J.: Replacement Lipomatosis of the Kidney, J. Urol. **34:** 296-301 (Oct.) 1935.
16. Kretschmer, H. L., and Pierson, L. E.: Fibrolipomatosis of the Kidney, Illinois M. J. **61:** 336 (April) 1932.
17. Peacock, H. A., and Balle, Alfred: Renal Lipomatosis, Ann. Surg. **103:** 395-401 (March) 1936.
18. Scandurra, Salvatore: Lipomatous Sclerosis of Kidney: Pathogenic Study of Case, Policlinico (sez. chir.) **39:** 765-775 (Dec. 15) 1932.
19. Gridnev, A.: So-Called Fatty Degeneration of Kidney, Ztschr. f. urol. Chir. **35:** 180-188, 1932.
20. Richards, E.: Remarks on the Fatty Transformation of the Kidney, Brit. M. J. **2,** 1883.
21. Griffon: Bull. Soc. anat. de Paris **71:** 481, 1896.
22. Browne, J. H.: Adipose Formation of the Kidney, Tr. Path. Soc. London **13:** 131, 1861-1862.

It is interesting to note that in the last thirty-seven cases reported, in twenty-five of which functional tests were performed, only five of the affected kidneys showed any function whatever. Thus, in 80 per cent of these twenty-five cases the kidney had been autonephrectomized. In twenty-one of the thirty-seven cases pyelography was attempted; in thirteen, or 62 per cent, of these twenty-one cases no pyelographic medium or only a very small amount could be injected into the pelvis.

Atrophic pyelonephritis as described by Braasch [23] and renal atrophy as described by Cumming and Schroeder [24] seem to be conditions essentially similar to that under consideration. Braasch reported twenty-eight cases; the patients' average age was 38, and none had nephrolithiasis. Cumming and Schroeder reported fifteen cases; the average age was 49, and 80 per cent of the patients had urinary stone. The important features of these conditions seem to be a decrease in the renal parenchyma, as a result of infection, and fibrous replacement, which follows. Although Cumming and Schroeder said little about deposition of fat, one of their illustrations is a beautiful example of fatty replacement. The average age in the reported cases of renal lipomatosis in which the figure is available is 46; in 76 per cent of the reported cases renal calculus was present. Most of the reporting authors have emphasized an infectious source. From these facts one might conclude that these variously described and named conditions are all different phases or manifestations of the same process. In all, destruction of renal tissue, usually by infection, is the primary factor; subsequent to this there is replacement by fat, fibrous tissue or both. In most cases of all types the condition is unilateral and of long duration, and most patients show great or complete loss of function of the involved kidney. We therefore suggest that all these conditions be classed together and described as renal atrophy with fibrous or with fatty replacement. Such a classification would greatly simplify the present complicated nomenclature.

23. Braasch, W. F.: Atrophic Pyelonephritis, J. Urol. 7: 247-257 (April) 1922.
24. Cumming, R. E., and Schroeder, C. F.: Renal Atrophy, J. Urol. 37: 407-436 (April) 1937.

REPORT OF CASES

An examination of the kidney specimens in the Museum of Pathology of the Ohio State University College of Medicine disclosed thirty-seven which showed a significant increase in the peripelvic fat. These were graded as to the degree of increase on the basis of 4, with 1 indicating the least amount of increase deemed to be abnormal and 4 indicating complete fatty replacement. The accompanying illustrations depict graphically the method of gradation. The specimens were stained with sudan IV for better demonstration of the fat, and the fat is therefore black in the illustrations.

The specimens are grouped in table 1 according to the nature of the underlying renal damage. The number of cases in each group is as follows: nephrosclerosis (hypertensive kidney) eight, pyelonephritis five, nephrolithiasis five, cloudy swelling five, tuberculosis three, chronic glomerulonephritis three, hypoplasia two, amyloidosis two, senile arteriosclerotic kidney two and hypernephroma two. Since the number of specimens of a given type of lesion in a museum varies widely both with the relative frequency of the lesion and with the collector's particular interests, these figures are felt to be of comparatively little importance.

Fig. 4 (case 4).—Nephrosclerosis, grade 3 replacement; sudan IV.

Fig. 5 (case 5).—Tuberculosis, grade 3 replacement, sudan IV.

Fig. 6 (case 6).—Senile arteriosclerotic kidney, grade 3 replacement; sudan IV.

In table 2 the cases are arranged according to the amount of fatty replacement present. The resulting figures are deemed to be more significant. It will be noted that the more severe grades of fatty increase occur with those conditions in which there is apt to be considerable destruction of renal parenchyma: nephrolithiasis, tuberculosis, nephrosclerosis, senile arteriosclerotic kidney, chronic glomerulonephritis, congenital hypoplasia and pyelonephritis.

The one case of grade 4 replacement and three of the cases of grade 3 replacement will be considered in some detail. The cases of grade 2 and of grade 1 replacement are included in the tables to show the rather wide variety of renal lesions which may be followed by fatty replacement and to show the comparative frequency of the milder degrees of this process. The cases of cloudy swelling and hypernephroma might at first seem to confuse the issue; however, although the specimens are good examples of these conditions

and are exhibited as such in the museum, the fatty replacement in each is due to some underlying destructive process, usually nephrosclerosis. It will be noted that none of these shows more than grade 1 replacement.

CASE 1.—M. G., a white woman aged 63, entered St. Francis Hospital Aug. 11, 1936, complaining of pain in the left flank of one and one-half years' duration. At the time of onset she had noticed increased frequency of urination, especially at night. Three months previous to admission she had noticed swelling in the left flank, which steadily increased in size. Since that time she had passed blood at frequent intervals. She had lost 70 pounds (32 Kg.) in the preceding twelve months and had had night sweats during the whole period. The past history was otherwise irrelevant.

TABLE 1.—*Underlying Renal Damage in Thirty-Seven Cases*

Diagnosis	Case No.	Degree of Fatty Increase	Average Degree of Fatty Increase per Group
Chronic glomerulonephritis			1.3
	7	2	
	20	1	
	19	1	
Nephrosclerosis			1.6
	21	1	
	8	2	
	9	2	
	22	1	
	23	1	
	24	1	
	5	3	
	10	2	
Cloudy swelling			1.0
	25	1	
	26	1	
	27	1	
	28	1	
	29	1	
Senile arteriosclerotic kidney			2.5
	6	3	
	11	2	
Amyloidosis			1.0
	30	1	
	31	1	
Hypoplasia			1.5
	32	1	
	12	2	
Pyelonephritis			1.8
	14	2	
	15	2	
	34	1	
	16	2	
	17	2	
Nephrolithiasis			2.6
	13	2	
	3	3	
	1	4	
	33	1	
	2	3	
Tuberculosis			2.0
	4	3	
	35	1	
	18	2	
Hypernephroma			1.0
	36	1	
	37	1	

The patient was fairly well developed and had a mass over the left flank about the size of an orange, which was slightly tender and fluctuant and somewhat movable. The blood pressure was 125 systolic, 80 diastolic; the temperature ranged from normal to 99.5 F.; the pulse rate was 75, and the respiratory rate was 20. A blood count showed erythrocytes 4,330,000, hemoglobin content 80 per cent, leukocytes 7,100, polymorphonuclears 79 per cent and lymphocytes 21 per cent. A catheterized specimen of urine had a specific gravity of 1.015, 4 plus white blood cells, an occasional red blood cell and 1 plus granular casts. The Wassermann reaction was negative, the nonprotein nitrogen content 28 mg. per hundred cubic centimeters and the sedimentation rate normal. A plain roentgenogram of the abdomen disclosed a calculus in the region of the left kidney; a chest plate gave negative results. Cystoscopic examination showed chronic cystitis. The right ureter was catheterized easily. There was an obstruction in the left ureter 2 cm. above the ureteral orifice. Indigo carmine appeared in three minutes in good concentration from the right kidney. No dye or urine could be obtained from the left kidney in forty-five minutes. The obstruction in the left ureter did not allow any sodium iodide to enter. Intravenous injection of neo-iopax showed a normal right kidney and a functionless left kidney. Urine from the right kidney showed 5 red blood cells, 8 white blood cells and 1 plus bacilli. Urine from the bladder showed 4 plus white blood cells, 1 plus bacilli and no acid-fast organisms. The diagnosis was functionless left kidney, with calculous pyonephrosis and perinephric abscess.

Five days after admission, with the patient under ether anesthesia, the perinephric abscess was drained (L. J. R.). Owing to the patient's poor condition on the table, nothing else was done. The wound was closed around an iodoform drain. The temperature rose from normal to 103 F. the first and second days. It was normal the third day and then rose to 104 F., where it remained until the death of the patient on the sixth day. A blood culture taken on the fourth postoperative day was negative. The leukocyte count two days after operation was 26,000, with 89 per cent polymorphonuclears.

The diagnosis at autopsy was nephrolithiasis on the left side; inflammatory destruction of the left kidney, with complete fatty replacement; chronic ureteritis on the left side, with stenosis; chronic cystitis; cholelithiasis, and toxic splenomegaly.

CASE 2.—V. R., a woman aged 49, entered University Hospital June 9, 1930, complaining of pain over the right lower quadrant and tenderness over the right lumbar area, chills and fever, and some urgency and frequency. There was no history of hematuria or stone. The pain over the right lower quadrant had been present for several years but had become acute in the three weeks preceding admission. The past history was otherwise irrelevant.

TABLE 2.—*Amount of Fatty Replacement in Thirty-Seven Cases*

Degree of Fatty Replacement	Case No.	Underlying Renal Damage
Four plus		
	1	Nephrolithiasis
Three plus		
	2	Nephrolithiasis
	3	Nephrolithiasis
	5	Tuberculosis
	4	Nephrosclerosis
	6	Senile arteriosclerotic kidney
Two plus		
	7	Chronic glomerulonephritis
	8	Nephrosclerosis
	9	Nephrosclerosis
	10	Nephrosclerosis
	11	Senile arteriosclerotic kidney
	12	Hypoplasia
	13	Nephrolithiasis
	14	Pyleonephritis
	15	Pyelonephritis
	16	Pyelonephritis
	17	Pyelonephritis
	18	Tuberculosis
One plus		
	19	Chronic glomerulonephritis
	20	Chronic glomerulonephritis
	21	Nephrosclerosis
	22	Nephrosclerosis
	23	Nephrosclerosis
	24	Nephrosclerosis
	25	Cloudy swelling
	26	Cloudy swelling
	27	Cloudy swelling
	28	Cloudy swelling
	29	Cloudy swelling
	30	Amyloidosis
	31	Amyloidosis
	32	Hypoplasia
	33	Nephrolithiasis
	34	Pyelonephritis
	35	Tuberculosis
	36	Hypernephroma
	37	Hypernephroma

Physical examination showed a fairly well nourished woman with marked kyphosis and scoliosis. There was tenderness over the right renal area, and an indefinite mass was felt in the right lumbar area. The temperature ranged from normal to 103 F. daily. The pulse rate varied from 90 to 120 daily; the respiratory rate was 20. Urinalysis showed a specific

gravity of 1.020, a 2 plus reaction for albumin, 4 plus white blood cells and no red blood cells. The phenolsulfonphthalein test showed 45 per cent elimination in the first hour and 10 per cent in the second hour. The nonprotein nitrogen content was 22 mg. per hundred cubic centimeters on June 10, 40 mg. on June 16 and 20 mg. on June 27. A blood count showed erythrocytes 3,480,000, hemoglobin content 38 per cent, leukocytes 7,800 and polymorphonuclears 73 per cent. The Wassermann reaction was negative. Cystoscopic examination revealed chronic cystitis; the bladder was otherwise normal. The ureters were catheterized easily. The urine from the right ureter contained 2 plus white blood cells and from 1 to 3 red blood cells; the urine from the left ureter contained from 4 to 6 white blood cells and from 3 to 5 red blood cells. Indigo carmine injected intravenously appeared in the urine from the left kidney in six minutes in excellent concentration but did not appear in the urine from the right kidney after one hour. A roentgenogram showed a stone in the region of the right kidney. The pyelogram of the right side showed a marked filling defect in the pelvis. The diagnosis was renal stone on the right side and pyonephrosis.

Ten days after admission the right kidney was drained and stones were removed by Dr. W. N. Taylor. Three days later the temperature fell to normal. Five days later a nephrectomy was performed by Dr. Taylor. The convalescence was uneventful and the patient was discharged July 17, 1930.

The removed kidney showed calculous pyonephrosis and practically complete gross and microscopic destruction of renal tissue, with replacement by fat and fibrous tissue.

CASE 3.—N. G., a woman aged 66, entered University Hospital June 8, 1931, complaining of pain in the right side, which had been present for twenty-three years, and hematuria, which had commenced six weeks previous to admission. She had had some frequency but gave no history of gravel, chills or fever. She had lost 50 pounds (23 Kg.).

Physical examination gave essentially negative results except that it showed a mass in the right upper quadrant, which extended from the costal margin to the level of the umbilicus and to the midline. This moved on respiration and was firm and slightly nodular. Cystoscopic examination disclosed chronic cystitis. The right ureteral orifice was edematous and injected. The bladder was otherwise normal. Indigo carmine appeared from the left ureter in five minutes in excellent concentration. No dye appeared from the right side in half an hour. Urine from the right kidney showed pus 3 plus; the urine from the left kidney was normal. The urine from the bladder showed from 50 to 60 leukocytes and 2 plus bacteria. The pyelogram of the right side showed a staghorn calculus with infection. A blood count showed red cells 2,750,000, hemoglobin content 48 per cent, leukocytes 24,950 and polymorphonuclears 91 per cent. The Wassermann reaction was negative. The diagnosis was calculus of the right kidney with pyonephrosis.

The patient was operated on under spinal anesthesia by Dr. Taylor. A curved right lumbar incision was made into the fatty capsule. The renal mass was very large and difficult to enucleate, owing to well organized adhesions. By removing the stone from the kidney and draining the pyonephrosis the size of the kidney was reduced and its removal was made easier. The pedicle vessels were tied individually, and the wound was closed in three layers around a gauze drain. The convalescence was uneventful, and the patient was discharged July 11.

The removed kidney was large; the pelvis was dilatated and contained several stones. There was marked destruction of renal parenchyma, with replacement by fat.

CASE 4.—G. M., a man aged 38, entered St. Francis Hospital Jan. 23, 1934, complaining of hemorrhage from the nose, shortness of breath and swollen ankles. He had nocturia, urinating from four to five times. His past history was irrelevant except for smallpox in 1928 and an injury to the left eye in 1932.

Physical examination showed a fairly well developed white man sitting upright in bed and evidently dyspneic. The head and the right eye were normal. The left eye showed fibrotic changes in the cornea; the left nostril contained a pledget of cotton saturated with blood. The teeth were carious. The heart was enlarged to the left, and the sounds were muffled.

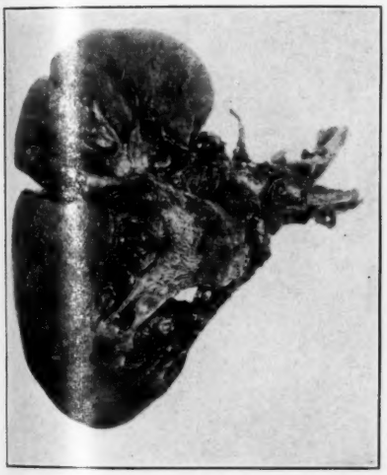

Fig. 7 (case 7).—Chronic glomerulonephritis, grade 1 replacement; sudan IV.

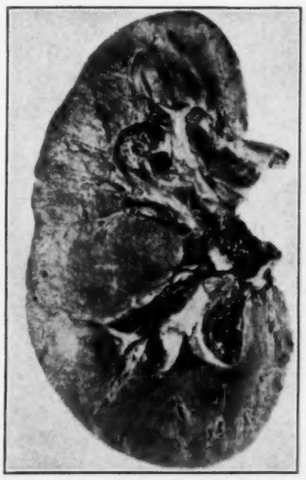

Fig. 8 (case 24).—Nephrosclerosis, grade 1 replacement; sudan IV.

Fig. 9 (case 30).—Amyloid disease, grade 2 replacement; sudan IV.

Fig. 10 (case 32).—Hypoplasia, grade 2 replacement; sudan IV.

The blood pressure was 220 systolic, 115 diastolic. The scrotum and legs were edematous. The urine showed a 4 plus reaction for albumin, an occasional white cell, an occasional granular cast, an alkaline reaction and a specific gravity of 1.013. A blood count showed red cells 2,250,000, hemoglobin content 40 per cent, white cells 7,750, polymorphonuclears 95, lymphocytes 4 and monocytes 1. The nonprotein nitrogen content was 60 mg. per hundred cubic centimeters. The Wassermann reaction was 4 plus. On February 12 the nonprotein nitrogen was 133 mg. The patient's condition grew steadily worse; purpuric spots developed on the neck and chest. He died March 28. The diagnosis was hypertensive cardiac decompensation, pneumonia of the lower lobe of the right lung and chronic glomerulonephritis.

The postmortem diagnosis was generalized arteriolar sclerosis, marked nephrosclerosis with fatty replacement of renal parenchyma, cardiac hypertrophy and lobar pneumonia.

COMMENT

In the seventy cases reported to date of replacement lipomatosis of the kidney a correct preoperative diagnosis has not been made. In most of these cases the diagnosis has been calculous pyonephrosis, tumor of the kidney, tuberculosis of the kidney or chronic glomerulonephritis. In each there was a history of infection over a long period.

There are no outstanding clinical symptoms to indicate the presence of replacement lipomatosis. There

may or may not be pain over the area of the kidney. The chronicity of the infection may produce pyuria with or without dysuria. The urine may be normal, because many affected kidneys are functionless and are accompanied by a normal kidney on the opposite side. The tests for blood chemistry and renal function

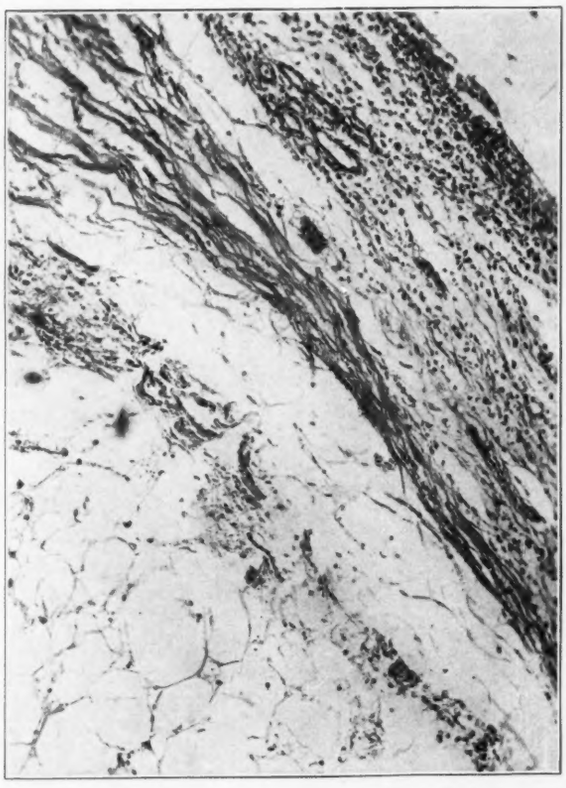

Fig. 11.—Fatty replacement due to pyelonephritis.

usually give normal results, because the condition is almost always unilateral. Since the advent of pyelography, in 62 per cent of the cases in which this procedure has been attempted a marked filling defect has been shown or else the ureteral obstruction has been such that little or no pyelographic medium could be injected. Tests of the renal function were performed in twenty-five cases, in 80 per cent of which the affected kidney was shown to be functionless. In 76 per cent of the reported cases a renal calculus was present.

When such conditions as chronicity of infection, renal calculus, functionless kidney and a marked filling defect in a pyelogram are found concomitantly one must suspect atrophy of the kidney with replacement lipomatosis. It is to be understood that these statements apply only to the condition generally termed replacement lipomatosis and are not applicable to fatty replacement complicating the various types of Bright's disease.

COMMENT ON PATHOLOGY

Although much has been written concerning fatty replacement of the kidney, the frequency of the milder degrees of this condition, the wide variety of underlying pathologic processes and the similarity of this state to certain other rather common types of tissue change have been largely overlooked. The major purpose of this paper is to emphasize phases of the problem.

The fact that thirty-seven examples of this condition were rather easily and quickly discovered in an average museum of pathology designed for teaching purposes should be ample evidence that the process, especially in its milder forms, is not uncommon. Furthermore, every pathologist performing routine autopsies is well acquainted with the fact that an increase in peripelvic fat commonly occurs in any situation in which the amount of renal parenchyma is severely decreased.

In this series of thirty-seven cases there are included (aside from hypernephroma and cloudy swelling, which are probably not primarily concerned) eight types of underlying pathologic process: nephrolithiasis, pyelonephritis, tuberculosis, chronic glomerulonephritis, nephrosclerosis, senile arteriosclerotic kidney, amyloidosis and congenital hypoplasia. Of these, four (nephrosclerosis, senile arteriosclerotic kidney, hypoplasia and amyloidisis) are definitely of noninflammatory origin, and one (chronic glomerulonephritis) is due not to the presence of bacteria in the kidney but to toxins formed elsewhere and acting on the kidney. Only three (nephrolithiasis, pyelonephritis and tuberculosis) are characterized by local infection. Furthermore, practically all the conditions which cause extensive destruction of renal parenchyma with concomitant decrease in renal bulk are included in this list. This should serve to illustrate rather clearly the point that the cause of the condition is specific only in that it implies destruction of renal tissue and decrease in the size of the renal mass.

Fig. 12.—Fatty replacement due to tuberculosis.

Briefly stated, there are five types of fatty change which should be mentioned in a discussion of this subject: fatty tumor or lipoma; fatty degeneration of parenchymatous tissues, representing probably merely a change in the nature of preexisting invisible fat so that it becomes visible; fatty infiltration, consisting of storage of fat such as is seen in obesity; lipoid histio-

cytosis, which is probably a constitutional or metabolic disturbance, and fatty replacement of inactive or destroyed tissue. Of these, we are concerned mainly with the one last mentioned. Numerous examples of situations in which fat replaces regressing parenchymatous tissue can be cited, of which only a few will be given here. One of the most obvious examples is seen in the varying relationship between fat, fibrous tissue and secretory tissue in the breast under physiologic conditions; the nonlactating female breast is made up largely of fat, the lactating breast is composed almost entirely of secretory epithelium and the breast after lactation returns to its previous fatty nature. Another example is seen in the bone marrow. The marrow of infants is abundant and red; in the adult the marrow of the long bones is normally almost entirely fatty; with the advent of a condition such as pernicious anemia the marrow of the long bones again becomes active in the formation of blood cells, and the fat disappears, only to reappear in the event of satisfactory treatment. The skeletal muscle of the extremities normally contains little visible fat; however, after amputation the muscles proximal to the point of amputation undergo a disuse atrophy and are largely replaced by fat. From these few citations it will be seen that one of the normal functions of fat is to fill in any otherwise unoccupied space and to act as padding.

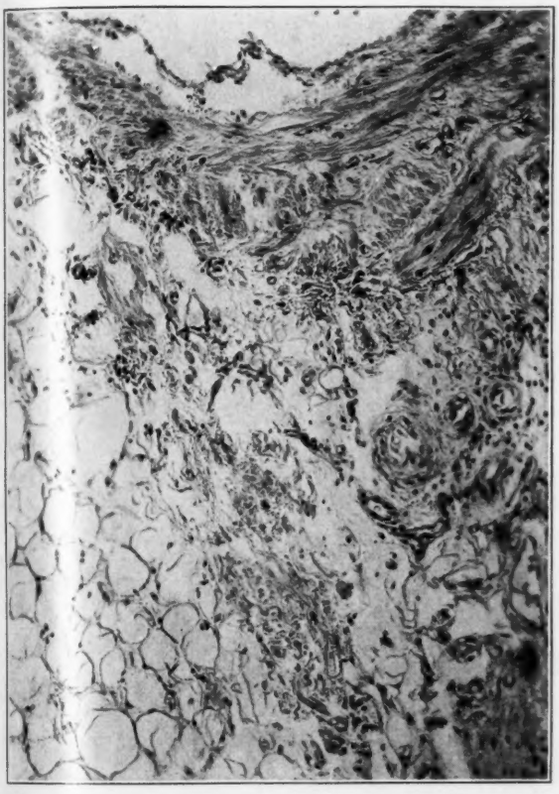

Fig. 13.—Fatty replacement due to nephrosclerosis.

Summarizing these various phases of the process into a single thesis, we see that the fundamental underlying cause of fatty replacement of the kidney is a decrease in the size or bulk of the kidney from any cause; that since there are many such causes this process is common and occurs under widely differing circumstances, and that the process is in keeping with the laws of the body as a whole and is not one peculiar to the kidney.

CONCLUSIONS

1. Fatty replacement of the kidney is not a rare condition.

2. It occurs as a result of any process which destroys renal tissue or otherwise decreases the bulk of the kidney.

3. Inflammation has no specific relationship to the causation of fatty replacement.

4. This situation is similar to many others frequently occurring elsewhere in the body, in which fat replaces a regressing parenchyma.

5. Thus far a clinical diagnosis has not been made preoperatively.

6. Chronicity of infection, the presence of renal calculus, a functionless kidney and a marked filling defect in the pyelogram occurring concomitantly should lead one to consider the possibility of the presence of fatty replacement of the kidney.

Clinical Notes, Suggestions and New Instruments

OSTEOMA OF FRONTAL SINUS AND PENETRATION OF LATERAL VENTRICLE, WITH INTERMITTENT PNEUMOCEPHALUS

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ALBANY, N. Y.

While some osteomas of the frontal and ethmoidal sinuses may long remain asymptomatic, many others have been observed to cause local pains and headaches. If the bony growth or an associated mucocele bulges into the cranial cavity, corresponding cerebral disturbances may follow. Pneumocephalus has been observed in several patients suffering with these tumors.[1] In one of Dr. Cushing's cases (reported by Armitage [2]) the mucocele had actually penetrated the lateral ventricle. Recently we have studied a similar case, in which

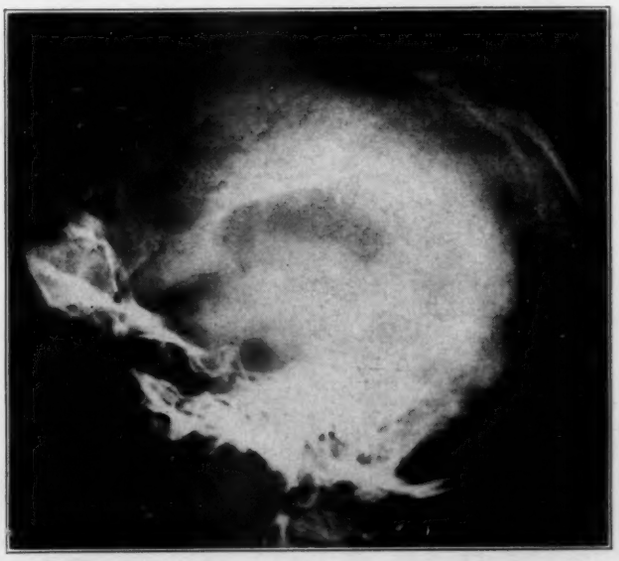

Fig. 1.—Osteoma of the left frontal sinus. The head is in the lateral position, and air may be seen in the left ventricle.

From the Department of Surgery of the Albany Medical College.

1. Cushing, Harvey: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, with Report of Four Cases, Surg., Gynec. & Obst. **44**: 721 (June) 1927. Payne, A. E., and Jeans, W. D.: Intracranial Pneumatocele, Brit. J. Surg. **23**: 679 (Jan.) 1936. Armitage.[2] Hoover and Horrax.[4]

2. Armitage, George: Osteoma of the Frontal Sinus, Brit. J. Surg. **18**: 565 (April) 1931.

the principal complaints were of general convulsions and headaches. Since this situation is apparently uncommon, we have ventured briefly to record our observations.

A. R., a white man, aged 26, a chauffeur, was admitted to the Albany Hospital on Dec. 29, 1936, complaining of con-

Fig. 2.—Appearance a few moments after that shown in figure 1, with the forehead rotated upward, showing the air to have passed out of the ventricle and to have collected in the subdural space.

vulsive attacks, of generalized headaches and of a noise "like water running" in his head. (He was referred to the medical service of Dr. Thomas Ordway by Dr. John Mosher of Coeymans, N. Y.) He had been in good health until fourteen

Fig. 3.—The osteoma after its piecemeal removal. The rulings are in centimeters.

months previously. At that time he began to have bouts of dull, bilateral, low frontal and retro-orbital pain, which occasionally radiated to the right ear and down the right side of the neck. Of late the headaches had become more severe and on several occasions had been accompanied by vertigo, by tinnitus in the right ear and by nausea and vomiting. They were notably aggravated by jolting and by stooping over. Shortly after the onset he commenced to hear a curious noise within his head, as of "water flowing," always from the front to the back. At times even his wife could hear this sound, particularly if he shook his head. There were long intervals when the "splashing" was not present.

Two months before he entered the hospital, violent generalized convulsions began. Since they always occurred during sleep, the patient was not aware of them, but the supra-orbital headaches were likely to be more severe the next morning. At about the same time his wife noticed some change in his personality, that he was becoming more irritable and quarrelsome.

Six weeks before he entered the hospital the headaches became particularly severe behind the left eye and in the left suboccipital region and were associated with constant nausea. The pain was worse when the patient sat up, so that he insisted on lying perfectly flat in bed, without even a pillow. A lumbar puncture then revealed clear, colorless spinal fluid, under no increase of pressure (130 mm. of water), a cell count of 2 and a total protein content of 46 mg. per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative. A roentgenogram of the skull taken at that time by Dr. W. P. Howard disclosed a large osteoma of the left frontal sinus. The tumor appeared to extend posteriorly for from 3 to 4 cm. and to have over it the displaced and thickened posterior wall of the sinus. A subsequent review of these films revealed no air within the cranial cavity.

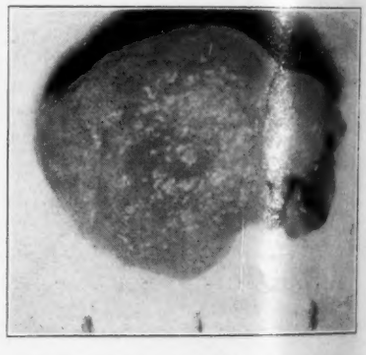

Fig. 4.—The posterior surface of the mucocele after its removal from the ventricle.

On examination at this time the patient was seen to be well developed, of good color, a little underweight and evidently in some distress. The pain was then principally behind the left eye, and he stated that he had been hearing the noise in his head recently. With the room perfectly quiet, a faint splashing sound could be heard distinctly when his head was quickly nodded. With the stethoscope this sound was most plainly audible in each temporal region.

The vital signs were normal, and the neck was not stiff. No external bony deformity of the skull was found. The left eye slit was perhaps a trifle narrower than the right; other than this, the general physical and neurologic examination revealed no abnormalities. The left eyeball was not protruded or rotated.

Roentgenograms made at this time with the head in the lateral position (fig. 1) revealed air in the lateral ventricles; when the head was rotated so that the forehead was up, the air was shown to have left the ventricles and to have collected outside the left frontal lobe and just above the osteoma (fig. 2).

A frontal osteoplastic craniotomy on the left side was performed (E. H. C.) on December 30, the anteriormost edge of the bone flap passing just above the frontal sinus. When the dura was retracted, the large osteoma was readily brought into view. At its upper margin there was a cone-shaped elevation surrounded by a collar of dura. When we attempted to obtain further exposure at this point, the dura suddenly separated from the osteoma, carrying within it most of a mucocele. The intracranial surface of the bony tumor was then completely exposed. It proved to have a broad attachment to the floor and the anterior wall of the sinus. Removal was accomplished piecemeal with chisel and gouge (fig. 3). The lateral portion of the sinus was filled with mucocele, which was carefully cleaned out. There was no sign of infection.

A vertical incision was then made in the dura, extending upward from the circular opening for about an inch. Some air escaped. A glistening, grayish mucocele with many small lobulations was seen bulging into the underlying brain. The original dural incision was then extended to include the

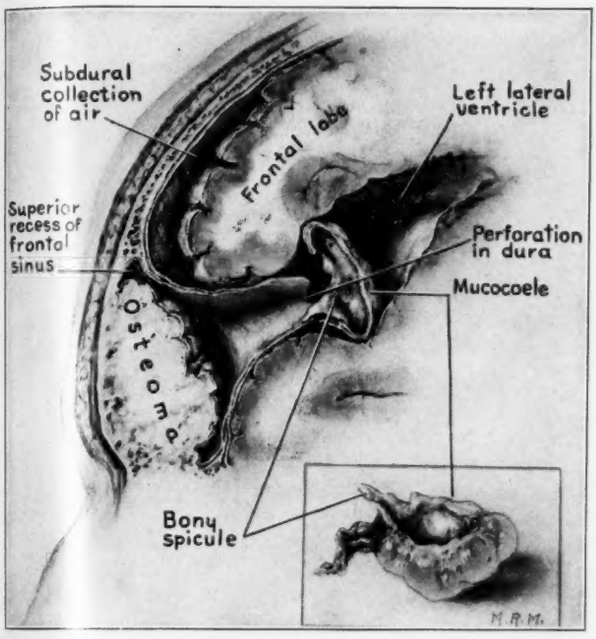

Fig. 5.—Semidiagrammatic drawing to show the osteoma of the left frontal sinus and its relation to the intraventricular mucocele.

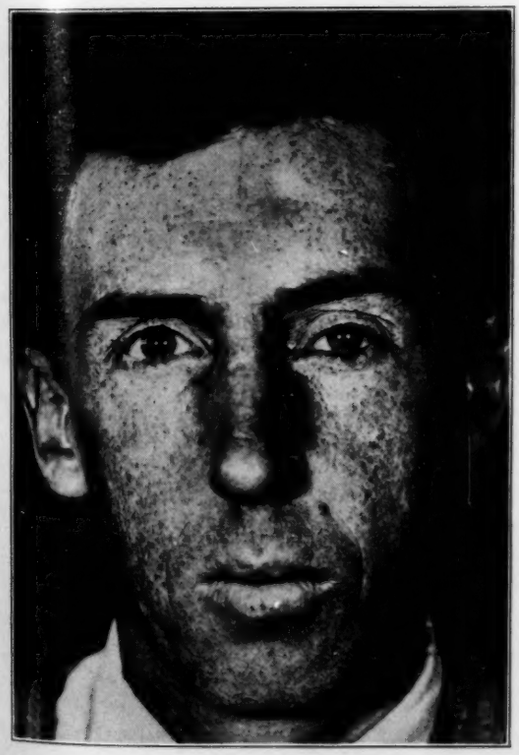

Fig. 6.—The patient twelve weeks after operation. The incision, being that employed for the removal of pituitary tumors, is largely concealed within the hairline.

collar of attached dura. When this was done, the entire tumor was readily lifted out of the frontal lobe. There were no adhesions between it and the brain, and no bleeding ensued.

On further inspection it was discovered that the hole made by the mucocele, and hence the latter itself (fig. 4), had extended directly into the anterior horn of the (left) lateral ventricle (fig. 5). The septum pellucidum and the foramen of Monro were plainly seen. The cortical arachnoid appeared to be continuous with the ependymal lining of the ventricle.

The dura was then completely closed, the defect being repaired with a small patch of temporalis fascia.

The convalescence was uneventful. In the fifteen months which has elapsed since the operation, the patient has had no headaches, no convulsions and no more of the curious sounds within his head.

COMMENT

Air is not infrequently found within the cranial cavity after a fracture through the paranasal sinuses. Dandy,[3] in discussing the surgical significance of pneumocephalus, pointed out the resulting danger both from infection and from increased intracranial pressure. He showed that closure of the dural defect prevented the reaccumulation of air and obviated further danger of meningitis.

The vagaries of orbito-ethmoidal osteomas have been related by Cushing.[1] His experience and subsequently that of Hoover and Horrax[4] showed the advisability of attacking these growths through an intracranial approach. The inward intrusion of the mucocele is seldom demonstrable by ordinary roentgenograms. Even in the absence of pneumocephalus or of neurologic signs and symptoms, it is not possible to be sure that an osteoma which involves the inner wall of the sinus has no intracranial component. Removal of the mass through the sinus may be difficult or even impossible, and the danger of carrying infection in is certainly great. In order, therefore, to deal adequately with the growth and its associated mucocele, if present, and in order securely to patch the dural opening, should one be found to exist, an osteoplastic craniotomy is essential. The incision may be placed entirely within the hairline, and no scar or deformity need result. The operation should carry with it a minimum of risk.

32 Willett Street.

FRACTURE OF THE OPTIC CANAL CAUSING OPTIC ATROPHY

EUGENE FREEDMAN, M.D., CLEVELAND

Roentgenologic visualization of the optic canal was first described in 1917 by de Kleyn and Stenvers.[1] The authors read an article by Rhese[2] demonstrating the visualization of the posterior ethmoid cells and the sphenoid sinuses on an oblique roentgenogram of the facial bones. Seeing the reproduction, de Kleyn and Stenvers realized that with slight modification Rhese's position could be utilized to demonstrate the optic canal. During the past few years roentgen technic of the optic canal has been simplified with the aid of excellent localizing devices developed by Pfeiffer[3] and by Camp and Gianturco[4] which eliminate the measurement of certain angles and various other haphazard elements of the technic.

The indications for roentgen examination of the optic canal are numerous, but the procedure is employed chiefly in primary and secondary diseases of the optic nerve in an attempt to demonstrate either diseased posterior ethmoid cells surrounding the optic canal, as the cause of a primary optic atrophy, or enlargement and destruction of the optic canal by a tumor of the optic nerve, or by an intracranial tumor growing into the orbit through the optic foramen.

The osseous canal normally affords great protection to the optic nerve, but during injuries to the head and eye, it may

3. Dandy, W. E.: Pneumocephalus, Arch. Surg. **12**: 949 (May) 1926.
4. Hoover, W. B., and Horrax, Gilbert: Osteomas of the Nasal Accessory Sinuses, Surg., Gynec. & Obst. **61**: 821 (Dec.) 1935.

From the Department of Roentgenology of the University Hospitals.

1. de Kleyn, A., and Stenvers, H. W.: Weitere Beobachtungen über die genauere Lokalisation der Abweichungen im Bereiche des Foramen opticum und der Ethmoidalgegend mit Hilfe der Radiographie, Arch. f. Ophth. **93**: 216, 1917.
2. Rhese: Die chronischen Entzündungen der Siebbein Zellen und der Keilbeinhöhle, Arch. f. Laryng. u. Rhin. **24**: 383, 1910-1911.
3. Pfeiffer, R. L.: A New Technique for Roentgenography of the Optic Canals, Am. J. Roentgenol. **29**: 410 (March) 1933.
4. Camp, J. D., and Gianturco, C.: A Simplified Technique for Roentgenographic Examination of the Optic Canals, Am. J. Roentgenol. **29**: 547 (April) 1933.

sustain a fracture, and this may be followed by an optic atrophy. The atrophy is caused either by the pressure of the depressed wall or by an intracanalicular hematoma. Occasionally a loose fragment of bone may pierce the optic nerve, leading to the development of atrophy. The first report of fracture of the optic canal associated with optic atrophy was published by Goalwyn[5] in 1926. The roentgenogram of the optic canal showed a fine fracture line extending from the sphenoidal fissure into the optic canal, and a hematoma was surmised to be the cause of the atrophy.

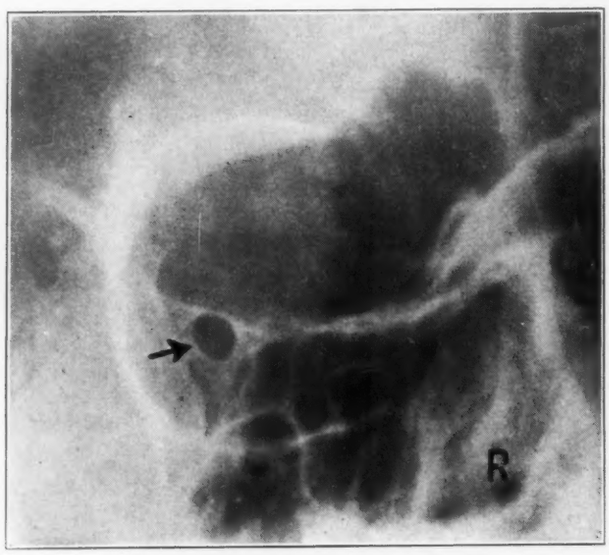

Fig. 1.—Normal optic canal on the right side.

According to my knowledge the case to be reported is the second one in which the cause of optic atrophy was a fracture of the optic canal:

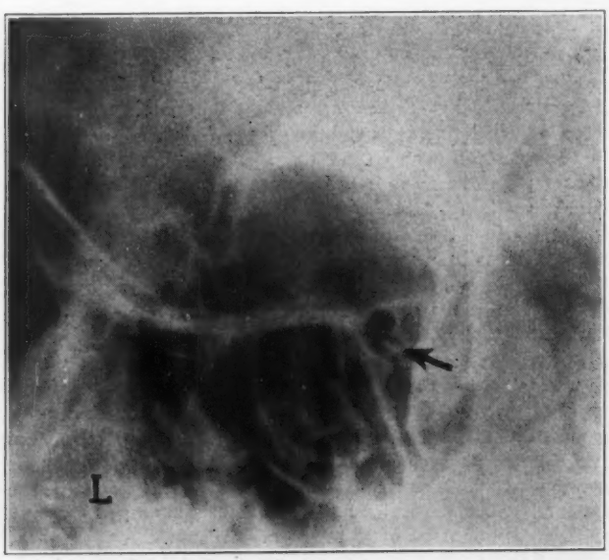

Fig. 2.—Depression of the lateral wall of the left optic canal and the tiny loose fragment of bone within the lumen of the canal.

E. H., a white man aged 46, admitted to the outpatient department of the University Hospitals Dec. 21, 1937, complained of blindness of the left eye of one year's duration. A year before the patient was thrown from an automobile onto the pavement in such a way that the running board came to rest on his head. The automobile had to be raised to free him. He received immediate treatment at another hospital.

As he regained consciousness he noted that there was no light perception in the left eye. He was told that there was a "blood clot" pressing on his eye.

Examination of the eyes on admission by Dr. Lorand V. Johnson revealed the following changes:

Examination with glasses: right eye, 6/7.5; left eye, no light perception.

Visual fields: right eye, normal; left eye, no light perception.

Right eye: pupil, tension, media and disk not remarkable. Left eye: no direct or consequential pupillary reflex and, with the right eye covered, an amaurotic nystagmus; media clear; very marked optic atrophy (probably secondary); macula and retina not remarkable.

Roentgen examination of the skull, facial bones and optic canal revealed a healed depressed fracture of the left zygoma and a wide linear fracture in the right occipital region measuring about 8 cm. in length and 3 mm. in width. The right optic foramen was round, was smooth in contour and measured about 6 mm. in diameter (fig. 1). The lateral wall of the left optic canal was depressed medially and in addition a loose fragment of bone measuring about 3 mm. in length and 1 mm. in width (fig. 2) was seen to lie within the lumen of the optic canal. It was concluded from this examination that the optic atrophy was caused partly by the pressure of the depressed wall of the lateral canal and partly by the loose fragment of bone, which had probably pierced the optic nerve.

The case is reported to call attention to the value of the special study of the optic canal in cases of trauma to the orbital region. This may be of great importance from the standpoint of a possible immediate exploration of the optic canal to free the nerve from the effects of pressure caused by a fracture of the walls.

2065 Adelbert Road.

5. Goalwyn, H. A.: The Clinical Value of Optic Canal Roentgenograms, Arch. Ophth. **55**: 1 (Jan.) 1926.

HEREDITARY MULTIPLE TELANGIECTASIS WITH EPISTAXIS

METHOD OF TREATMENT

GEORGE HUNTER O'KANE, M.D., MED. SC.D., NEW YORK

Hereditary multiple telangiectasis with epistaxis, known also as Rendu-Osler-Weber disease, is a syndrome in which the terminal vessels, the capillaries and the venules become dilated.[1] On microscopic examination these dilated vessels are found to have a single layer of endothelial cells covered by a very thin epithelium.[2] As a result of this peculiar anatomic construction, these vessels readily become dilated and bleed profusely following the slightest trauma.

These lesions appear grossly as small red or purplish spots, usually occurring on the nasal mucosa of the septum and turbinates and sometimes occurring on the oral mucosa and skin as seen in this patient.[2] It is known that the telangiectases may occur anywhere in the skin or mucous membranes and may become manifest as hematuria, gastrointestinal bleeding, uterine bleeding or epistaxis.[1]

This disease, unlike hemophilia, may be transmitted by either sex and may affect either the male or the female.[3] Unlike hemophilia, the bleeding and coagulation time are normal.

The diagnosis depends on three factors: (1) a history of repeated hemorrhages, (2) a history of familial occurrence and (3) the discovery of telangiectatic lesions in the mucous membranes.

LITERATURE

In reviewing the recent literature on the subject, one author suggests that telangiectases may occur in the brain or viscera, causing early death.[4] This has some bearing on this case,

From the Service of John D. Kernan, M.D., Columbia-Presbyterian Medical Center.

Read before the New York Academy of Medicine, Section of Otolaryngology, Jan. 19, 1938.

1. Pearlman, S. J.: Heredofamilial Telangiectasis or the Rendu-Osler-Weber Disease, Arch. Otolaryng. **23**: 257 (Feb.) 1936.
2. Houser, K. M.: Congenital Multiple Hemorrhagic Telangiectasia, with Epistaxis, Arch. Otolaryng. **20**: 438 (Sept.) 1934.
3. Osler, William: Cong. Hem. Telangiectases, Bull. Johns Hopkins Hospital **12**: 330, 1901.
4. Piszkiewicz, F. J.: Hereditary Multiple Telangiectases, Arch. Otolaryng. **17**: 429 (March) 1933.

since all the patient's siblings died in infancy and may have been afflicted with this disease.

It has been noted by others that epistaxis caused by this disease has an unexplained tendency to cause hemorrhage in the spring and autumn months.[5] It has also been observed

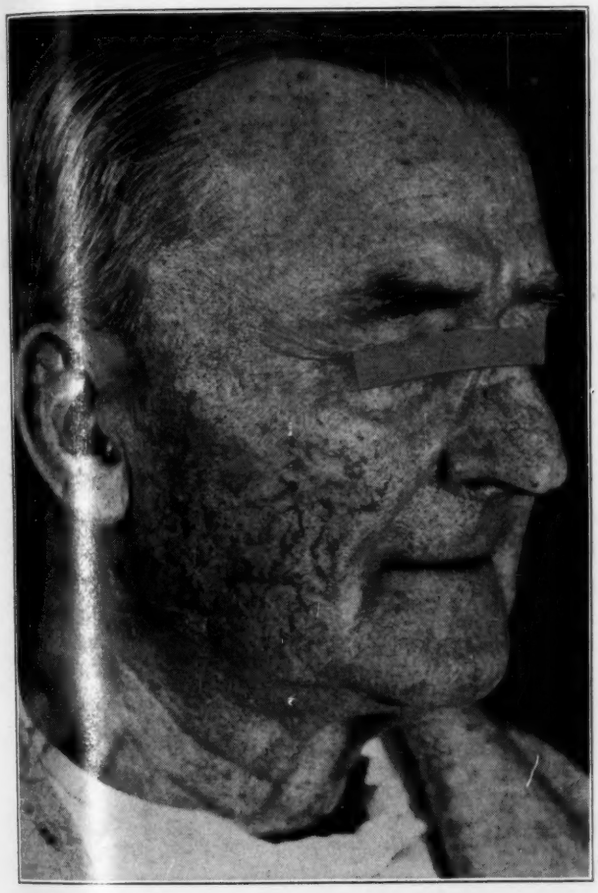

Fig. 1.—Right side of face showing numerous spider telangiectases.

that hemorrhages tend to become more frequent and severe toward middle age.[2] As I shall point out later, this was true of this patient.

In the world's literature there are reports of eighty-five families in which the disease has occurred, although the disease is probably more common than these figures indicate.[6]

METHODS OF TREATMENT

Methods of treatment have included the galvanocautery, diathermic coagulation, the application of escharotics such as silver nitrate, chromic acid bead and trichloroacetic acid. Radium has also been used. Radium makes the lesions friable and is apt to precipitate bleeding.[2] It has also been reported to have caused destruction of the cartilage of the nasal septum.[2] The difficulty with all these methods is that direct attack on the dilated vessels invariably produces severe hemorrhage that is difficult to control.

The method of treatment that we found successful in this case, after the methods mentioned had failed, is based on an indirect approach to the lesions. A fine pointed needle such as one uses to anesthetize the tonsillar area is introduced under the normal mucous membrane adjacent to the dilated vessel and enough 5 per cent quinine and urethane solution is injected to raise a small bleb alongside the vessel. The nose is then packed firmly over the injected area, which procedure allows the solution to diffuse into the vessel and obliterate it. In this way one avoids hemorrhage, which invariably ensues if one tries to inject directly into the vessel or to apply escharotics or coagulation directly. The type of packing that we have found most suitable for this purpose is half inch bismuth glycerin gauze packing. The packing may be removed in twenty-four hours.

It is advisable to attempt obliteration in several sittings, since the method is apt to be painful and to produce a local reaction. Moreover, one must bear in mind the possibility of idiosyncrasy to quinine.

It is interesting to note that in this case no new nevi arose at the site of previous injections. As new nevi do arise they can be destroyed before they cause epistaxis.

REPORT OF CASE

F., a man, aged 71, has had frequent nosebleeds since childhood. His father also suffered from frequent and severe epistaxis. The patient's nosebleeds became more severe at the age of 18 after a fracture of the nose. From this time until he was 43, he allowed the hemorrhages to continue until they stopped spontaneously. When he was 43 the bleeding increased in severity and frequency, so that he sought medical aid. Within a period of two years he underwent nine intranasal operations, including almost complete removal of the septum. The bleeding was not relieved. It recurred at frequent intervals, lasting from two to four hours.

Three years before admission to Vanderbilt Clinic, he received radium treatment at a nose and throat hospital in New York. During the treatment he suffered a severe epistaxis, which was controlled with difficulty and necessitated transfusion.

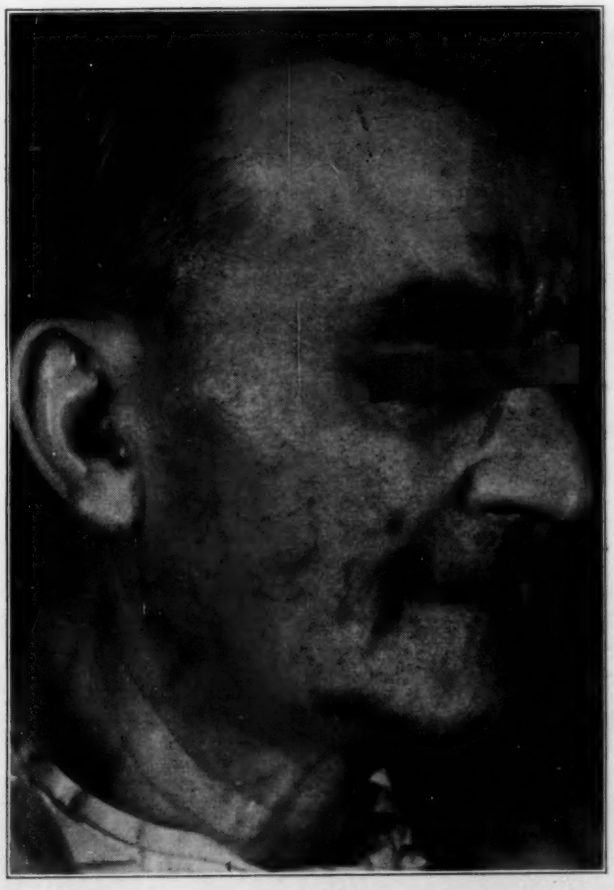

Fig. 2.—Right side of face under infra-red rays, showing telangiectases deep in skin.

When first seen in Vanderbilt Clinic Feb. 28, 1934, he had his nose packed with cotton. On removal of the cotton a severe nasal hemorrhage ensued. The nose was immediately repacked with bismuth gauze, which controlled bleeding. On admission to the Presbyterian Hospital the packing was removed and large purplish dilated vessels were observed on the lateral nasal

5. Schmitt, H.: Hereditary Hemorrhagic Telangiectases, Ztschr. f. Laryng., Rhin., Otol. **22**: 28 (Dec.) 1931.
6. Woodman, DeGraaf, and Opin, Edward: Personal communications to the author.

walls and the remains of the septum. When an attempt was made to electrocoagulate one of them, a drenching hemorrhage occurred, precluding further examination or treatment at that time. On each subsequent removal of packing, severe hemorrhage occurred. Dr. Maurice Lenz, chief of the department of radio therapy, was consulted and agreed to try radiotherapy. A 10 mg. radium tube in petrolatum gauze was placed in the right side of the nose and a 12.5 mg. tube was inserted in the left naris. This treatment did not obliterate the lesions and was abandoned at the suggestion of Dr. Lenz.

Among other consultants, he was seen by Drs. J. G. Hopkins and Beatrice Kesten of the department of dermatology and Dr. G. U. Carneal of the surgical staff. At their suggestion a 5 per cent solution of quinine and urethane was injected as described. This treatment was carried out with apparent obliteration of the larger lesions from March 7 to March 19, 1934. The patient was discharged with bleeding arrested.

During his stay in the hospital the stool gave a ++++ guaiac test; proctoscopic examination was negative. The melena, we believe, was due to swallowed blood, for when the nasal bleeding was controlled the stool gave a negative guaiac test. The bleeding time was three and one half minutes; the clotting time was three minutes. Hemoglobin at this time was 50 per cent; red blood cells numbered 3,100,000. The blood pressure was 140 systolic and 90 diastolic. The Wassermann reaction of the blood was negative.

Clinical examination showed varicosities on the face, in the nose and under the tongue. As far as could be ascertained, no other skin or mucous areas were affected.

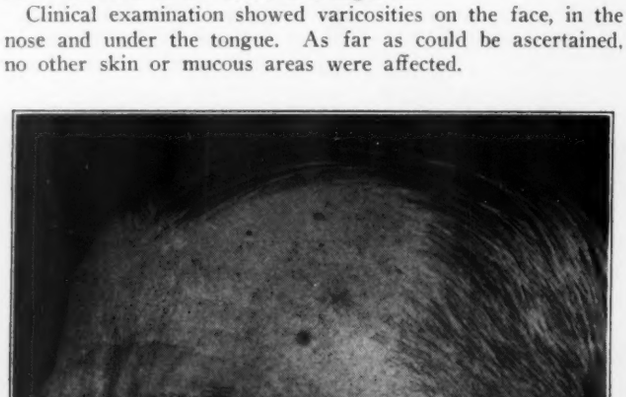

Fig. 3.—Left side of face showing surface spider telangiectases and round nevi.

From March to June 1934 he had eleven more injections with definite diminution in the severity of the hemorrhages, with the exception of one severe epistaxis May 24. For two months after this he was free from hemorrhages. Then from August 11 to October 1 he had a series of hemorrhages which were readily controlled in the clinic. Feb. 8, 1935, he bled again. The bleeding was not severe, however. During the following ten months he required only five injections. When seen Dec. 20, 1935, there were no lesions visible. No injection was required.

Since that time, more than two years ago, he has been almost entirely free from epistaxis. The slight bleeding that has occurred has been readily controlled with a light cotton plug.

Fig. 4.—Left side of face under infra-red rays, showing deep spider telangiectases and nevi.

During the past two years he has cut out alcohol and tobacco, and he drinks only one cup of coffee a day. It has been his impression in the past that these drugs seem to have precipitated bleeding.

SUMMARY AND CONCLUSIONS

1. Submucous injection of quinine and urethane, 5 per cent solution, presents a simple and effective means of controlling hereditary multiple telangiectasis with epistaxis, a troublesome and dangerous disease.

2. Vasodilators such as alcohol and stimulants such as coffee should be forbidden in the treatment of these patients.

3. This condition is not amenable to surgery.

116 East Fifty-Third Street.

Linnaeus, Physician and Botanist.—That Linnaeus was a graduate physician is not well known, yet he practiced medicine with great success, and as professor of medicine at Uppsala contributed much to medical teaching in Sweden at a time when the standards of medical education were at low ebb. In botany, he reigns supreme and is regarded by the world of science as one of the greatest naturalists of all time. He is often spoken of as the King of Flowers. . . . Carolus Linnaeus was born in southern Sweden on May 23, 1707, the first child of a country minister.—Larsson, B. Hjalmar: Carolus Linnaeus, Physician and Botanist, *Ann. M. Hist.* **10**:197 (May) 1938.

Special Article

VITAMIN A

METHODS OF ASSAY AND SOURCES IN FOOD

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This article and others recently published or to be published comprise a new series on the present status of our knowledge of the vitamins. They have been prepared under the general auspices of the Council on Pharmacy and Chemistry and the Council on Foods. The opinions expressed are those of the authors and not necessarily the opinions of either council. Reprints are not available but the articles will be published later in book form.—ED.

The early recognition of the significance of vitamin A as an essential constituent of the diet of man made the quantitative as well as the qualitative identification of food sources an important problem for investigators engaged in research on nutrition. Although vitamin A was one of the first, if not the first, of the vitamins to be discovered, accurate quantitative methods of analysis have been slow of development. This can be explained by the fact that, although its chemical identity had been established with reasonable certainty, synthesis of the vitamin and its separation in crystalline form was accomplished only recently.[1] The situation has been further complicated by the necessity for adopting a device for expressing vitamin A potency, since obviously the values could not be expressed in terms of vitamin A. In some of the early studies attempts were made to find some product that might serve as a standard, but it soon became apparent that the vitamin A content of natural foods was so variable that the chances of finding a suitable substance were remote. Several "units" accordingly were suggested.

After the discovery had been made that carotene is converted into vitamin A by the animal organism, the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations selected a well defined sample of carotene as the International Standard of Reference.[2] Although the selection of a substance of standard vitamin A potency has now been achieved, the preferred method of assay is still unsettled. In general the methods proposed are of three types: the so-called biologic methods, based on the behavior of laboratory animals; the color tests, and the more recently developed spectrographic, or absorption, methods. The biologic methods include the growth test; the ophthalmia test, based on the cure or prevention of the typical ocular condition due to a deficiency of vitamin A, and the vaginal smear test, which makes use of the irregular estrus and the appearance of cornified cells in the vaginal epithelium in vitamin A–deficient animals. The method of assay to be selected is dependent on the nature of the vitamin A activity, that is, on whether this activity is due to vitamin A itself, to provitamin A or to both, in the substance to be examined. The present discussion of methods will cover (1) the biologic methods, including the test based on the growth of rats and the vaginal smear test, (2) the color test with antimony trichloride and (3) the spectrographic method. The "growth" method is at present the official method of the U. S. Pharmacopeia[3] and it will be described first.

1. Wilke, Carl: Vitamin A Has Been Synthesized by Kuhn, Indust. & Engin. Chem., News. Ed. **29**: 291 (July 10) 1937. Holmes and Corbet.[6a]
2. League of Nations, Health Organisation: Second Conference on Vitamin Standardisation, London, June 12-14, 1934, Quart. Bull. Health Organ., League of Nations **3**: 428 (Sept.) 1934.

BIOLOGIC METHODS OF ASSAY

Early studies showed that the growth of experimental animals is proportional to the vitamin A content of the diet. It was also shown that vitamin A is concerned with the prevention and cure of a specific pathologic condition.

The Growth Method.—The assay of vitamin A by the growth method was introduced as early as 1920.[4] As developed and applied in various laboratories, this method embodies the following essential features: Young rats reared on a diet supplying vitamin A sufficient for growth and reproduction but not sufficient to permit excess storage are restricted to a diet which contains all the nutrients needed for growth except vitamin A. They are maintained on this diet long enough to reduce their body store of vitamin A until it will no longer support growth (preliminary, or depletion, period). The animals are then housed individually, and each is fed a specified daily allotment of the test material, as a supplement to the basal diet, throughout a period of several weeks (test period). During this time they are weighed at regular intervals, and there is a final weighing at the termination of the test. The increase in weight, or the growth response of the animal, obtained by subtracting from the final weight the weight on the day the first supplemental feeding was given, may then be used as a measure of the quantity of vitamin A ingested. Comparable, or matched, lots of animals given different quantities of vitamin A–containing material show growth graded to the dose. The relation between gain in weight and vitamin A intake is not linear but may be represented by a curve. This relationship has been rather extensively studied by Coward; she has derived formulas for the curve, which she calls the curve of response.[5]

The growth method has been refined and standardized until it is possible to obtain results with it that have as high a degree of accuracy as can be expected of procedures in which animals are used as reagents. The details of the method as applied by different investigators lend themselves, however, to a variety of interpretations, since rules acceptable to the majority have not been established. Consideration must be given not only to selection of a basal diet devoid of vitamin A and adequate in all other factors but to such questions as age, weight and dietary history of the experimental animals; acceptable weight limits of animals at the end of the depletion period; criteria for determining when the animals are depleted and suitable for the test; length of test period required for reliable results; relative significance of results with males and with females; effect of feeding the supplements in multiples of the daily dose at periodic intervals rather than in single daily doses; number of test animals required in an assay group assigned a given quantity of test material

3. United States Pharmacopeial Convention: The Pharmacopeia of the United States of America, Eleventh Decennial Revision, 1935.
4. Drummond, J. C., and Coward, Katharine H.: Researches on the Fat-Soluble Accessory Factor (Vitamin A): VI. Effect of Heat and Oxygen on the Nutritive Value of Butter, Biochem. J. **14**: 734 (no. 6) 1920. Osborne, T. B., and Mendel, L. B.: Nutritive Factors in Plant Tissues: IV. Fat-Soluble Vitamine, J. Biol. Chem. **41**: 549 (April) 1920.
5. Coward, Katharine H.; Key, Kathleen M.; Dyer, F. J., and Morgan, Barbara G. E.: The Determination of Vitamin A, Biochem. J. **24**: 1952 (no. 6) 1930. Coward, Katharine H.: The Relation of the Growth Response to Dosage of Vitamin A: Confirmation of a Curve Relating Response to Dose of Vitamin A Given, ibid. **28**: 865 (no. 3) 1934. Coward, Dyer, Morton and Gaddum.[14]

in order that the average gain in weight may be accepted as reliable; number of groups of experimental animals receiving graded doses of supplement required to establish the relation between vitamin A intake and gain in weight. Because most of these variables affect the accuracy of the results obtained, it seems advisable to consider the results reported in regard to them.

The vitamin A–free diet in most common use consists of casein extracted with a suitable fat solvent or subjected to prolonged heating [6] to render it vitamin A-free, vitamin A–free starch, yeast to supply the water-soluble growth-promoting factors and a suitable salt mixture. Vitamin D may be supplied by irradiation of the oil, the starch or a portion of the yeast or through the daily administration of small quantities of irradiated cholesterol or ergosterol. Recently some investigators have added a vitamin A–free fat or oil carrying the growth-promoting unsaturated fatty acids.[7] Linseed oil or corn oil may be used for this purpose.

The colony from which the experimental animals are obtained should be maintained on a diet containing enough vitamin A to support growth and reproduction but not enough to permit excess storage by the young. Otherwise the depletion period will be unduly long and the animals will be too large when depleted. The time required for depletion may be kept at a minimum by giving mother and young the vitamin A–free food during the lactation period [8] or, if the mother's diet contains whole milk (powder), by substituting skimmed milk (powder) during some portion of the lactation period.[9] Animals suitable for test purposes are described on the basis of weight at the time of weaning,[10] or on the basis of weight at the end of the depletion period.[11] The best results seem to be obtained with animals weighing between 70 and 90 Gm. when depleted. Animals weighing more than 100 Gm. are generally considered unsuitable. Criteria for judging when the depletion period should be terminated cannot be given categorically but to a certain extent must be established by the investigator for the colony of animals with which he is working. The animals should show stationary or declining weight and may or may not have acquired ophthalmia. In any case, symptoms of extreme vitamin A deficiency should not be present.[12] The length of the test period used depends on the accuracy desired, the reliability increasing in general the longer the test is continued, at least up to eight weeks.[13] Male and female test animals cannot be used interchangeably at all levels of vitamin A intake. At the low levels they show similar rates of gain, but at higher levels the males grow faster.[14] Nine or ten animals in an assay group seem to be sufficient to give results that may be considered reliable,[15] although this number may vary somewhat according to the rate of gain [16] and the sex of the animals, twice as many females as males being required for the same degree of reliability.[17] The number of assay groups required to establish the relation between gain in weight and vitamin A intake depends on the reliability of the results from each group and the accuracy desired. Three points are naturally the least that can be used, and four or five are probably sufficient. The vitamin A supplements are generally specified in terms of the daily dose. The results seem to be the same, however, whether this is fed daily or in multiples of the daily dose at less frequent intervals.[18]

Interpretation of Results.—As already stated, the growth method was in use several years before the adoption of the International Standards of Reference for vitamins A, B_1, C and D. During that time several units were proposed for expressing vitamin A activity in terms of the measurements made. The one most extensively used was perhaps the Sherman, or the Sherman-Munsell, unit, sometimes called the rat-growth unit. This unit was defined as that amount (of vitamin A) which when fed daily (six times a week) just sufficed to support a rate of gain of 3 Gm. a week in a standard test animal (rat) during an experimental feeding period of from four to eight weeks.[19] To obtain values in terms of this unit, it was customary to use at least three groups of comparable ("matched") test animals: one to receive a daily supplement of test material designed to support the standard rate of gain of 3 Gm. a week, one to receive a quantity of supplement somewhat less than this and the third to receive a quantity somewhat larger. At the end of the test the average gain in weight for each group was calculated, and a curve was drawn relating quantity of test food ingested to gain in weight. The quantity of test material required to support a gain in weight of 3 Gm. a week was then derived from this curve. The reciprocal of this value (expressed in grams) indicated the number of "rat growth" units of vitamin A per gram of material.

Although the rat growth unit was soon recognized as of little use for expressing absolute vitamin A values, the 3 Gm. a week rate of gain is often used as representative of the most reliable and most sensitive portion of the curve relating gain in weight of rats to vitamin intake.

Since adoption of the International Standards of Reference [20] for the vitamins it has been advisable to carry out biologic assays in such a way that the quantitative estimates derived from the results may be expressed in terms of international units rather than

6. Todhunter, E. N.: A Comparison of Heated Casein with Extracted Casein in the Basal Diet for the Determination of Vitamin A, J. Nutrition **13**: 469 (May) 1937.

7. Evans, H. M., and Lepkovsky, Samuel: Vital Need of the Body for Certain Unsaturated Fatty Acids: III. Inability of the Rat Organism to Synthesize the Essential Unsaturated Fatty Acids, J. Biol. Chem. **99**: 231 (Dec.) 1932.

8. Nelson, E. M.: Regulating the Storage of Vitamin A in Animals That Are to Be Used for the Determination of This Vitamin, Science **68**: 212 (Aug. 31) 1928.

9. Unpublished data, United States Department of Agriculture, Bureau of Home Economics.

10. Nelson.[8] U. S. Pharmacopeia.[3]

11. Sherman, H. C., and Burtis, M. P.: Factors Affecting the Accuracy of the Quantitative Determination of Vitamin A, J. Biol. Chem. **78**: 671 (Aug.) 1928.

12. Norris and Church.[43] U. S. Pharmacopoeia.[3]

13. Irwin, Margaret H.; Brandt, A. E., and Nelson, P. Mabel: Applications of Statistical Method to the Data of Vitamin Feeding Experiments: I. The per Cent. Effect of Measured Variables, J. Biol. Chem. **88**: 449 (Sept.) 1930. Sherman and Burtis.[11] Coward.[16] Norris and Church.[43]

14. Coward, Katharine H.; Dyer, F. J.; Morton, R. A., and Gaddum, J. H.: The Determination of Vitamin A in Cod Liver Oils (*a*) Biologically, (*b*) Chemically, (*c*) Physically, with a Statistical Examination of the Results, Biochem. J. **25**: 1102 (no. 4) 1931. Sherman and Burtis.[11]

15. Sherman, H. C., and Batchelder, E. L.: Further Investigation of Quantitative Measurement of Vitamin A Values, J. Biol. Chem. **91**: 505 (May) 1931. Coward, Dyer, Morton and Gaddum.[14] Coward and Key.[18]

16. Coward, Katharine H.: The Influence of the Length of the Test Period on the Accuracy Obtainable in a Vitamin A Test, Biochem. J. **27**: 445 (no. 2) 1933. Irwin, Brandt and Nelson.[13]

17. Coward, Katharine H.: Variation in Growth Response of Rats in Vitamin A Tests Compared with the Variation in Rats Growing Normally, Biochem. J. **26**: 691 (no. 3) 1932.

18. Coward, Katharine H., and Key, Kathleen M.: Simplification of Vitamin Tests: The Effect of Giving Doses Half-Weekly for Vitamin A Tests, and Once Only for Vitamin D Tests, Instead of Giving Doses Daily, Biochem. J. **28**: 870 (no. 3) 1934.

19. Sherman, H. C., and Munsell, Hazel E.: The Quantitative Determination of Vitamin A, J. Am. Chem. Soc. **47**: 1639 (June) 1925.

20. A detailed discussion of the selection of the international standard carotene and the use of a selected sample of cod liver oil as a subsidiary standard is given in a Special Report of the Medical Research Council. Information on the selection of a suitable solvent for the standard is included. This material, presented by Hume and Chick,[57] has been summarized by E. V. McCollum (The Fat-Soluble Vitamins, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1936, p. 379).

in terms of "rat growth" units.[21] Failure to give serious attention to the necessity of considering devices for making accurate comparisons with the international standards has in many instances led to the derivation of estimates that were far from the true values. Two methods of carrying out assays to obtain exact values in terms of international units have been suggested and described in detail.[22]

Attempts have been made to derive a factor for converting vitamin A values expressed in Sherman or rat growth units to equivalent values expressed in international units.[22] In this connection it is essential to emphasize the fact that the rat growth unit has no absolute value in terms of vitamin A and that, therefore, the derivation of a conversion factor is not a valid procedure. Any implied relationship must be considered as merely indicative. Values have appeared in the published literature from time to time, to be sure, but these have included extremes of 0.5 and 1.5 and there has been no basis for selecting one in preference to another. As a matter of fact, for some data reported one factor would probably more nearly serve the purpose, while in other cases the value at the other extreme might better be used.

The illogic of attempting to derive a single conversion factor of this sort may be illustrated by a consideration of factors suggested by results obtained during the past year[23] with positive control animals used in vitamin A assays on various products. All of these animals were given daily during a five week test period an amount of U. S. P. reference oil estimated to supply 1 international unit of vitamin A on the basis of the vitamin A value claimed for this oil. A total of sixty-five litters of animals were represented and all were drawn from the colony especially maintained for vitamin A assay work. Since in assays of this kind results with six to ten animals are generally considered sufficient to give an average that may be accepted as reliable, average gains in weight were derived for groups made up respectively of the controls taken from eight litters in order of the date of birth of the animals. The resulting average gains in weight for the eight groups established in this way were 18.0, 33.5, 30.3, 23.5, 16.4, 17.3, 31.3 and 28.3 Gm. By reference to a dose-effect curve for cod liver oil these were estimated to represent approximately the following vitamin A values in Sherman (Munsell) units: 0.9, 2.5, 2.1, 1.4, 0.8, 0.9, 2.2 and 1.9. On the basis of these results, therefore, the number of Sherman (Munsell) units equivalent to 1 international unit might be anything between 0.8 and 2.5. The use of another dose-effect curve might give slightly different values for Sherman units, of course, but the average gains in weight still stand as evidence of the variability in the value of the "growth unit" even in tests carried out with presumably "standard" animals.

The Single-Feeding Growth Method.—The growth method as usually carried out involves the feeding of supplements at periodic intervals during several weeks and the estimation of quantitative values from the gain in weight of the animals during the test period. A somewhat modified form of this technic is the so-called single feeding method, in which a single dose of vitamin A–bearing material is given to vitamin A–depleted animals. In this case the survival of the animals is proportional to the vitamin A content of the material fed.[24] By measuring the area under the curve relating weight to survival days of animals fed different materials, it is possible to compare the vitamin A potency of these materials.[25] This method was recently successfully applied in the assay of pasture grasses.[26]

The Vaginal Smear Method.—Female rats deprived of vitamin A show abnormal estrus and the presence of cornified cells in the vaginal epithelium.[27] This condition, which is one of the first and most pronounced evidences of a lack of vitamin A, clears up directly on the administration of vitamin A. Studies have been made to determine whether this phenomenon could be made the basis of a quantitative method.[28] Although the method developed has several distinct advantages, it does not commend itself for general adoption, because of the rather tedious procedure and the difficulty involved in interpreting the results quantitatively.[29]

CHEMICAL AND PHYSICAL METHODS

As information was accumulated on the chemical and the physical characteristics of vitamin A, certain properties were identified that offered possibilities as bases for methods of quantitative analysis. The more extensively studied methods include the color tests, particularly the blue color reaction with antimony trichloride, and methods based on the selective absorption shown by vitamin A and vitamin A compounds. Although the reaction with antimony trichloride is no longer considered to have possibilities as the basis of a specific and dependable quantitative method, it may be used for certain routine purposes of control and therefore will be reviewed briefly. The spectrographic method of analysis holds promise of eventually becoming an accepted technic for quantitative work, although it is still largely in the investigative stage.

The color test and the spectrographic method do not apply to the determination of vitamin A activity due to the carotenoid precursor. No attempt will be made in the limited space allotted to this paper to discuss the blue reaction with antimony trichloride or the spectrographic technic as applied to the determination of the carotenoid precursors. The international unit,

21. The Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations at its 1931 conference (Report of the Conference on Vitamin Standards, London, June 17-20, 1931, Geneva, 1931, p. 68) adopted a specially prepared sample of carotene as the International Standard of Reference for vitamin A. A unit of vitamin A (international unit) was then defined as the vitamin A activity of 1 microgram of this international standard. During the interval from 1931 to 1934, when the next conference was held,[2] it was learned that the various forms of carotene do not possess the same vitamin A activity, β-carotene being more active than either α-carotene or γ-carotene. Accordingly, at the 1934 international conference a sample of pure β-carotene was adopted to replace the 1931 standard, which had been shown to be a mixture. The sample of β-carotene had been carefully assayed against the old standard, and from the average results from several laboratories, 0.6 microgram was accepted as equivalent to 1 microgram of the 1931 standard. The international unit of vitamin A is therefore the vitamin A activity of 0.6 microgram of pure β-carotene.

22. Daniel, Esther P., and Munsell, Hazel E.: Vitamin Content of Foods: A Summary of the Chemistry of Vitamins, Units of Measurement, Quantitative Aspects in Human Nutrition, and Occurrence in Foods, Misc. Pub. 275, United States Department of Agriculture, Bureau of Home Economics, 1937.

23. Unpublished data, Bureau of Home Economics, United States Department of Agriculture.

24. Sherman, H. C., and Cammack, M. L.: A Quantitative Study of the Storage of Vitamin A, J. Biol. Chem. **68**: 69 (April) 1926. Nelson, E. M.; Walker, Reed, and Jones, D. B.: Determination of Vitamin A by a Preventative Method, J. Biol. Chem. **92**: vi (June) 1931.

25. Sherman, H. C., and Todhunter, E. N.: The Determination of Vitamin A Values by a Method of Single Feedings, J. Nutrition **8**: 347 (Sept.) 1934.

26. Hodgson, R. E., and Knott, J. C.: The Method of Single Feeding as Used in Measuring the Vitamin A Activity of Pasture Grass Artificially Dehydrated at Different Temperatures, Am. Dairy Sc. A. West. Div. 22d Annual Meeting Proc., 1936, p. 41.

27. Evans, H. M., and Bishop, K. S.: On the Existence of a Hitherto Unrecognized Dietary Factor Essential for Reproduction, Science **56**: 650 (Dec. 8) 1922.

28. Macy, Icie G.; Outhouse, Julia; Long, M. Louisa, and Graham, Alice: Human Milk Studies: I. Technique Employed in Vitamin Studies, J. Biol. Chem. **73**: 153 (May) 1927. Coward, Katharine H.: The Influence of Vitamin A Deficiency on the Oestrous Cycle of the Rat, J. Physiol. **67**: 26 (Feb. 28) 1929. Coward, Katharine H.; Morgan, Barbara G. E., and Dyer, F. J.: II., ibid. **69**: 349 (May) 1930.

29. Baumann, C. A., and Steenbock, Harry: The Vaginal Smear Method of Determining Vitamin A, Science **76**: 417 (Nov. 4) 1932.

on the other hand, is defined in terms of the international standard, which is β-carotene. Thus it is not possible to interpret results from the color test or the spectrographic technic directly in terms of international units by comparison with results of concurrent tests on the international standard. It is necessary to use conversion factors giving the relation between the potency of vitamin A expressed in international units as determined by the biologic method and the constant for vitamin A of the chemical or physical property being measured. In several reports in which conversion factors are discussed, values determined by the biologic method and expressed in terms of international units are referred to as "biologic values." This expression should not be confused with the Sherman, or rat growth, unit of vitamin A, which is sometimes called the biologic unit.

The Color Test with Antimony Trichloride.—As early as 1920 [30] it was suggested that the color reaction of cod liver oil with concentrated sulfuric acid might be related to the vitamin A content. Systematic investigations soon identified several color reagents, including arsenic trichloride,[31] which gave a brilliant ultramarine color with cod liver oil. The evidence obtained seemed to support the conclusion that this reaction was specific for vitamin A. A number of the color reagents were investigated by Carr and Price,[32] who gave particular attention to conditions necessary for the determination of quantitative relationships. Of the reagents studied, antimony trichloride in chloroform solution was the most satisfactory. The authors gave detailed directions for carrying out the test, and for this reason it is often referred to as the Carr-Price color test. As a quantitative method it has been used chiefly with liver oils, concentrates and extracts. In applying the test to the assay of oils,[33] a 20 per cent solution of the oil in chloroform is prepared at a given temperature, usually 20 C. Of this solution 0.2 cc. is placed in a glass cell having an internal measurement of 1 cm., and the cell is placed in a colorimeter or tintometer designed for matching the color against standard glasses. Two cc. of antimony trichloride reagent (antimony trichloride in dry chloroform saturated at 20 C.) is added so that the two solutions mix. The blue color develops rapidly and then fades. Readings are taken as the color develops, the point of maximum intensity being taken as the correct value. The values read are usually expressed as blue units, or Lovibond blue units.

Intensive studies of the antimony trichloride reaction with oils have shown that the color produced is not proportional to the amount of oil used, i. e., to the concentration of vitamin A.[34] The color reaction is not a linear function of vitamin A concentrations of oil. Furthermore, there seems to be no uniformity in the type of curve relating concentration of oil to color produced.[35] Results obtained with the unsaponifiable fraction, on the other hand, give a more nearly linear relationship.[36] These values also check satisfactorily with values obtained by the biologic method.[37]

Certain plant pigments, including carotene, are known to give a blue color reaction with antimony trichloride. The reaction with carotene may be differentiated from that with vitamin A by heating the solutions on a water bath at 60 C. The blue color with carotene will persist, while that with vitamin A changes to rose, violet-red or wine-red, according to the concentration of vitamin present.[38]

The blue reaction with vitamin A is more stable at low temperatures [39] and may be stabilized by the addition of hydroquinone [40] or guaiacol.[41] Certain other substances interfere with the reaction. A large number of these have been identified and tabulated according to the maximum quantity that may be present without masking the test.[42]

Interpretation of Results.—The relation of the Lovibond blue unit to the Sherman unit of vitamin A has been variously given. The wide discrepancies in the following factors indicate the futility of attempting to select a conversion factor:

1 Sherman unit = 2.18 Lovibond blue units [35]

10 Sherman units (eight week test) = 7.1 and 8.2 Lovibond blue units.[43]

An attempt to establish a factor for interpreting results in terms of international units fares little better. The rich concentrate of vitamin A studied by Carr and Jewell [44] gave a value of 78,000 Lovibond blue units per gram and approximately 1.6×10^6 international units per gram, 1 Lovibond blue unit equals approximately 20 to 22 international units.

Other work [45] indicates a ratio of 20 to 1 for the vitamin A of a distilled oil, and for a natural oil the ratio is about 40 to 1. The crystalline vitamin A recently described by Holmes and Corbet [46] gave a blue value of 100,000 units per gram and has since been reported to contain approximately 3×10^6 international units per gram, giving a relation of 1 blue unit equals 30 international units.

Spectrographic, or Absorption, Methods.—Use of the spectroscope has recently come to the fore as an important method of analysis, especially for the identification of substances occurring in such small quantities as to defy the ordinary methods of quantitative chemical

30. Rosenheim, Otto, and Drummond, J. C.: On the Relation of the Lipochrome Pigments to the Fat-Soluble Accessory Food Factor, Lancet **1**: 862 (April 17) 1920.

31. Rosenheim, Otto, and Drummond, J. C.: A Delicate Colour Reaction for the Presence of Vitamin A, Biochem. J. **19**: 753 (no. 4) 1925.

32. Carr, T. H., and Price, E. A.: Colour Reactions Attributed to Vitamin A, Biochem. J. **20**: 497 (no. 3) 1926.

33. Antimony Trichloride Test for Cod Liver Oil, British Pharmacopeia, 1932, p. 596.

34. Wokes, F., and Willimott, S. G.: A Study of Antimony Trichloride as a Possible Quantitative Reagent for Vitamin A, Analyst **52**: 515, 1927. Norris, E. R., and Danielson, I. S.: Comparison of Biological and Colorimetric Assays for Vitamin A as Applied to Fish Oils, J. Biol. Chem. **83**: 469 (Aug.) 1929. Norris and Church.[35]

35. Norris, E. R., and Church, A. E.: A Study of the Antimony Trichloride Color Reaction for Vitamin A: II. The Dilution Curve of Cod Liver Oil with Antimony Trichloride Reagent, J. Biol. Chem. **87**: 139 (May) 1930.

36. Norris, E. R., and Church, A. E.: A Study of the Antimony Trichloride Color Reaction for Vitamin A: I. J. Biol. Chem. **85**: 477 (Jan.) 1930. Smith, E. L., and Hazley, Violet: The Reaction of Antimony Trichloride with Cod Liver Oil and Its Unsaponifiable Fraction, Biochem. J. **24**: 1942 (no. 6) 1930. Coward, Dyer, Morton and Gaddum.[14] Wise and Heyl.[37]

37. Wise, E. C., and Heyl, F. W.: Vitamin A Colorimetric and Biological Assay, J. Am. Pharm. A. **21**: 1142 (Nov.) 1932. Andersen, A., and Nightingale, E.: Test for Vitamin A in Margarine, Butter, and Other Fatty Foods, J. Soc. Chem. Ind. **48**: 139T (June 14) 1929. Coward, Dyer, Morton and Gaddum.[14] Norris and Church.[36] Smith and Hazley.[30] Lathbury.[45]

38. Andersen, A. C., and Levine, V. E.: Reaction to Differentiate Vitamin A from Carotene by Means of Antimony Trichloride, Proc. Soc. Exper. Biol. & Med. **32**: 737 (Feb.) 1935.

39. Ender, Fredrik: The Reaction of Fish-Liver Oils with Antimony Trichloride, Biochem. J. **26**: 1118 (no. 4) 1932.

40. Huston, R. C.; Lightbody, H. D., and Ball, C. D., Jr.: Some Biochemical Relations of Phenols: II. The Effect of Hydroquinone on the Vitamin A Content of Stored Oils, J. Biol. Chem. **79**: 507 (Oct.) 1928.

41. Rosenthal, Eugene, and Erdelyi, John: Some Remarks Concerning the New Colour Reaction of Vitamin A, Biochem. J. **29**: 2112 (Sept.) 1935.

42. Corbet, Ruth E.; Geisinger, Helen H., and Holmes, H. N.: Substances Which Interfere with the Antimony Trichloride Test for Vitamin A, J. Biol. Chem. **100**: 657 (May) 1933.

43. Norris, E. R., and Church, A. E.: A Study of the Antimony Trichloride Color Reaction for Vitamin A: V. Evaluation of a Colorimetric Unit on the Basis of the Biological Unit for Vitamin A, J. Nutrition **5**: 495 (Sept.) 1932.

44. Carr, F. H., and Jewell, William: Characteristics of Highly Active Vitamin A, Nature **131**: 92 (Jan. 21) 1933.

45. Lathbury, Kathleen C.: Vitamin A Determination: Relation Between the Biological, Chemical and Physical Methods of Test, Biochem. J. **28**: 2254 (no. 6) 1934.

46. Holmes, N. H., and Corbet, Ruth E.: A Crystalline Vitamin A Concentrate, Science **85**: 103 (Jan. 22) 1937.

analysis. If a substance shows selective absorption with characteristic maximums, it is a relatively simple matter to detect its presence and by determining the degree of absorption to obtain an estimate of the quantity present. This method has been applied in the case of vitamin A and vitamin A compounds with considerable success and promises to become an accepted method of analysis. For the most part the conventional types of equipment suitable for determining and measuring absorption in the visible and in the ultraviolet have been used, and the results have accordingly been referred to as spectroscopic, spectrographic or spectrophotometric measurements, according to the instrument employed.

Absorption of the Blue Antimony Trichloride–Vitamin A Compound.—The compound formed by antimony trichloride with the vitamin A of liver oils shows two absorption bands, with maximums near 606 and 572 millimicrons, respectively.[47] In the case of concentrates there may be considerable shift toward the red end of the spectrum, the maximums appearing near 617 and 583 millimicrons, although on dilution to give a vitamin A potency equivalent to that of cod liver oil the shift is not apparent.[48] It has been suggested that liver oils may contain two chromogens giving a blue color with antimony trichloride, one showing the maximum at 606 millimicrons and the other the maximum at 572 millimicrons.[49] Under suitable conditions both of these bands are present. It is possible, however, by changing the concentration or the temperature or by adding certain chemicals to alter these conditions so that either one or the other of these bands, but not both, is shown.[50] There is still some difference of opinion as to the specificity of these bands for vitamin A.[51]

The difference in behavior of the 617 millimicron and the 583 millimicron bands of the concentrates may be construed to indicate lack of homogeneity in vitamin A concentrates unless a satisfactory explanation of the difference is found.[52]

Absorption of Vitamin A.—In 1925 Takahashi[53] described a highly active vitamin A preparation (biosterin) showing selective absorption in the ultraviolet with a maximum in the region of 320 millimicrons. Subsequent studies on oils and concentrates showed a high correlation between the vitamin A content as determined by the biologic method and absorption in the region having a maximum at 328 millimicrons.[54] In the case of oils, however, not all of the absorption at 328 millimicrons is due to vitamin A. The extraneous absorption varies from oil to oil and in one case was shown to be as high as 40 per cent.[55] Reliable data therefore are obtained only by making the test with the unsaponifiable fraction. Although the measurement of absorption in the ultraviolet gives a good indication of vitamin A activity, there are still certain discrepancies that must be explained before the method can be generally adopted.[56]

Application of the Spectrographic Method to the Quantitative Estimation of Vitamin A.—As implied in the foregoing discussion, the spectrographic method for vitamin A involves measurement of absorption in the region of the spectrum where vitamin A or vitamin A compounds show selective absorption. The measurement is usually made at or near the maximum of the particular absorption band used. This value expressed as a fraction of the value for 100 per cent vitamin A then indicates the proportion of vitamin A present. The validity of this relationship depends on whether Beer's law holds for all concentrations of vitamin A; i. e., whether the ratio of the coefficient of absorption to vitamin A concentration is a constant for all concentrations of vitamin A. In the application of the test this has been assumed to be the case.

It has become customary in work with vitamin A to determine the coefficient of absorption on the basis of a 1 per cent solution of 1 cm. depth. The values are usually expressed as $E_{1\text{ cm.}}^{1\%}$, where E represents the optical constant, $\log \frac{I_o \text{ (intensity of incident light)}}{I \text{ (intensity of emergent light)}}$. The wavelength at which the determination is made must be indicated. This value is sometimes referred to as the specific absorptive index or the extinction coefficient.

When the extinction coefficient has been determined either for direct absorption in the ultraviolet in the region from 320 to 330 millimicrons or for the antimony trichloride blue compound at either of the two maximums specific for this compound, the next problem is to convert the reading into vitamin A potency in terms of international units. To do this it is necessary to know the value for international units per gram divided by the index coefficient for 100 per cent vitamin A, which is the factor by which the coefficient of absorption must be multiplied to obtain the vitamin A potency in international units. Reference has already been made to the rich concentrate of vitamin A described by Carr and Jewell.[44] This substance was shown to have coefficients of absorption for the blue reaction of $E_{1\text{ cm.}}^{1\%}$ 617 millimicrons = 5,000 and $E_{1\text{ cm.}}^{1\%}$ 580 millimicrons = 2,600 and a coefficient of absorption for absorption in the ultraviolet of $E_{1\text{ cm.}}^{1\%}$ 328 millimicrons = 1,600. Six ten-thousandths of a milligram contained slightly more than 1 international unit; i. e., the substance had a biologic

47. Drummond, J. C., and Morton, R. A.: Observations on the Assay of Vitamin A, Biochem. J. **23:** 785 (no. 4) 1929. Coward, Katharine H.; Dyer, F. J., and Morton, R. A.: The Determination of Vitamin A in Cod Liver Oils, (*a*) Biologically, (*b*) Chemically, (*c*) Physically, with a Statistical Examination of the Results: II. Further Evidence That the Intensity of Absorption at 328 Millimicrons Gives the Best Agreement with the Biological Measure of Vitamin A in Cod Liver Oils, ibid. **26:** 1593 (no. 5) 1932. Morton, Heilbron and Thompson.[48] Coward, Dyer, Morton and Gaddum.[54]

48. Morton, R. A.; Heilbron, I. M., and Thompson, Albert: Spectrographic Data Concerning Vitamin A and Liver Oils, Biochem. J. **25:** 20 (no. 1) 1931. Heilbron, I. M.; Heslop, R. N.; Morton, R. A.; Webster, E. T.; Rea, J. L., and Drummond, J. C.: Characteristics of Highly Active Vitamin A Preparations, ibid. **26:** 1178 (no. 4) 1932.

49. Gillam, A. E., and Morton, R. A.. The Antimony Trichloride Colour Test and the Ultraviolet Absorption of Liver Oils and Concentrates, Biochem. J. **25:** 1346 (no. 4) 1931. Heilbron, I. M.; Gillam, A. E., and Morton, R. A.: Specificity in Tests for Vitamin A: A New Conception of the Chromogenic Constituents of Fresh and Aged Liver Oils, ibid. **25:** 1352 (no. 4) 1931. Brode and Magill.[50] Morton.[52]

50. Brode, W. R., and Magill, Mary A.: A Critical Study of the Antimony Trichloride Color Test for Vitamin A, J. Biol. Chem. **92:** 87 (June) 1931. Morton.[52]

51. Magill, Mary A., and Brode, W. R.: A Comparison Between the Spectrophotometric and Biological Assay for the Vitamin A Content of Fish Liver Oils, Ohio J. Science **33:** 127 (March) 1933. Coward, Dyer, Morton and Gaddum.[54] Drummond and Morton.[47] Gillam and Morton.[49] Brode and Magill.[50] Morton.[52] Morgan, Edisbury and Morton.[56]

52. Morton, R. A.: The use of 7-Methylindole in the Antimony Trichloride Colour Test for Vitamin A, Biochem. J. **26:** 1197 (no. 4) 1932.

53. Takahashi, K.; Nakamiya, Z.; Kawakami, K., and Kitasato, T.: On the Physical and Chemical Properties of Biosterin (a Name Given to Fat-Soluble A) and on Its Physiological Significance, Inst. Phys. Chem. Res. (Tokyo) Sc. Papers **3:** 81 (no. 32) 1925.

54. Morton, R. A., and Heilbron, I. M.: The Absorption Spectrum of Vitamin A, Biochem. J. **22:** 987 (no. 4) 1928. Macwalter, R. J.: Some Factors Which Affect the Assay of Vitamin A by the Spectrographic Method, Biochem. J. **28:** 472 (no. 2) 1934. Coward, Dyer, Morton and Gaddum.[54] Drummond and Morton.[47]

55. Crews, S. K., and Cox, S. J.: The Relationship between the Carr-Price Value and the 328 Millimicron Absorption Coefficient of Preparations Containing Vitamin A, Analyst **59:** 85 (Feb.) 1934. Coward, Dyer, Morton and Gaddum.[54]

56. Morgan, R. S.; Edisbury, J. R., and Morton, R. S.: A Discrepancy Between Biological Assays and Other Methods of Determining Vitamin A: I. Biochem. J. **29:** 1645 (July) 1935. Pritchard, Harry; Wilkinson, Harry; Edisbury, J. R., and Morton, R. A.: II. ibid. **31:** 258 (Feb.) 1937. Wilkie.[60]

value between 1.6 and 2 million units per gram. On the basis of these constants the ratio

$$\frac{\text{biologic value (international units per gram}}{E\ {}^{1\%}_{1\ cm.}\ 328} = \frac{\text{1.6 to 2 million international units per gram}}{1{,}600}$$

would give a factor of approximately 1,250.

Other factors have been similarly determined on the basis of measurements made on rich concentrates of vitamin A. Those proposed up to 1935 are reviewed by Chick and Hume,[57] who give the accepted value for the conversion factor as 1,600. A more recent report by Hume [58] indicates that this factor is still the most satisfactory one to use.

From results of assays of fish liver oils by the biologic and spectrographic methods, Emmett and Bird [59] stated the conclusion that the ratio of

$$\frac{\text{international units per gram}}{E\ {}^{1\%}_{1\ cm.}\ 328 \text{ millimicrons}}$$

for vitamin A is "close to 2,000." In the case of concentrates the conversion factor varied with the quantity of alkali used in saponification.

Reference has already been made to the report of Holmes and Corbet [46] on the separation of crystalline vitamin A. This substance gave a value for $E\ {}^{1\%}_{1\ cm.}$ 328 millimicrons of 2,000. If the biologic value proves to be 3,000,000 international units, as tentatively reported, the conversion factor would be nearer 1,500 than 1,600.

The validity of the choice of the factor 1,600 or, for that matter, of any fixed factor for converting spectrographic readings to international units has been discussed by Wilkie.[60]

The determination by British investigators of the vitamin A in butter may be cited as an example of the application of the spectrographic method to the quantitative estimation of vitamin A.[61]

Special Instruments.—The type of equipment generally used in spectrophotometric work is expensive and requires, furthermore, a skilled operator to obtain accurate results. Early in 1933 Adolph Hilger, Ltd., London, placed on the market a simplified form of the spectrophotometer, called the vitameter. This instrument, which has been described by Irish,[62] is made especially for the assay of vitamin A and is calibrated to give $E\ {}^{1\%}_{1\ cm.}$ 328 millimicron values directly. A study of results obtained with the vitameter has been made by Wilkie,[60] who recommended that persons using the instrument interpret the readings by means of a dilution curve determined for the reference cod liver oil.

A modified spectrophotometer for the assay of vitamin A was recently described by McFarlan, Reddie and Merrill.[63] This instrument is small and compact, is claimed to be easy to operate and to give results in a minimum of time, about one and one-half minutes being required for a reading. The readings are given directly for log $\frac{I_o}{I}$ at 330 millimicrons, the wavelength of the monochromatic light used. A value of 1.32 for $E\ {}^{1\%}_{1\ cm.}$ 330 millimicrons for the U. S. P. reference cod liver oil was obtained. On the basis of 3,000 international units per gram given for this oil, the conversion factor for changing readings to international units was derived as 2,270.

FOOD SOURCES OF VITAMIN A

The study of food sources of vitamin A claimed the attention of investigators from the very time of discovery of this vitamin. As a result, considerably more data have accumulated on the occurrence of this factor in foods than is the case with some of the other vitamins. This material has been brought together in a publication recently issued by the United States Department of Agriculture [22] and will not be reviewed in detail here.

Foods are often classified from the standpoint of vitamin potency as fair, good or excellent sources, without any clear indication as to the actual meaning of these terms. In order to have uniform terminology in the Bureau of Home Economics for expressing relative significance of foods as sources of vitamins, these qualitative terms have been tentatively defined by limiting values expressed in Sherman units per hundred grams. The bases of the definitions are given here so that there may be no uncertainty as to the meaning of the text that follows. A food source containing 19 or less Sherman units of vitamin A per hundred grams was rated an insignificant source. From 20 to 99 units was considered fair; from 100 to 999 units, good; from 1,000 to 10,000 units, excellent, and over 10,000 units, outside the class of an ordinary food. The limiting value for excellent was selected on the basis of the richest food sources. The lower limit for good was then chosen so that foods in this class would supply a significant proportion of the day's requirement. These descriptive terms should not be interpreted too categorically, for it is necessary to take into account the quantity of the food usually eaten.

In considering quantitative values it is essential to remember that a single value allotted to any food must be treated as a selected representative value within the range of variation of different samples. The more the vitamin activity of foods is studied the more patent it becomes that in most cases there exists a wide variation from sample to sample even when the effective factors are controlled as far as possible.

In foods of plant origin there seems to be a direct parallel between greenness—chlorophyll content—and vitamin A activity. Although it is known that plant tissue owes its vitamin A activity to the presence of carotene, the relation, if any, between the presence of chlorophyll and the formation of carotene is not yet clear.

Thin green leaves are among the best sources of vitamin A, many of the fresh leaves assaying well over 1,000 units (Sherman) per hundred grams and some even as high as from 20,000 to 30,000 units. The parallelism between vitamin A content and greenness is made more apparent by a study of the relative vitamin A content of green and of bleached leaves from the same plant. The outer green leaves of iceberg lettuce, which are usually removed before the head is offered to the consumer, have been shown, for instance, to be from thirty to forty times as rich in vitamin A

57. Hume, E. Margaret, and Chick, Harriette: Reports on Biological Standards: IV. The Standardisation and Estimation of Vitamin A, Medical Research Council, Special Report Series, no. 202, London, His Majesty's Stat. Off., 1935.

58. Hume, E. M.: Estimation of Vitamin A, Nature **139:** 467 (March 13) 1937.

59. Emmett, A. D., and Bird, O. D.: Comparative Biological Value of Vitamin A as an Alcohol and Ester, J. Biol. Chem. **119:** xxxi (June) 1937.

60. Wilkie, J. B.: Report on Vitamin A: Determinations with the Hilger Vitameter, J. A. Off. Agric. Chem. **20:** 208 (May) 1937.

61. Morton, R. A., and Heilbron, I. M.: Vitamin A of Butter, Biochem. J. **24:** 870 (no. 4) 1930. Gillam, A. E.; Heilbron, I. M.; Morton, R. A.; Bishop, Gerald, and Drummond, J. C.: Variations in the Quality of Butter, Particularly in Relation to the Vitamin A, Carotene, and Xanthophyll Content as Influenced by Feeding Artificially Dried Grass to Stall-Fed Cattle, ibid. **27:** 878 (no. 3) 1933. Gillam, A. E.; Heilbron, I. M.; Ferguson, W. S., and Watson, S. J.: Variations in the Carotene and Vitamin A Values of the Milk Fat (Butter) of Cattle of Typical English Breeds, ibid. **30:** 1728 (Sept.) 1936.

62. Irish, F. W.: Report on Vitamin A: Determinations with the Hilger Vitameter, J. A. Off. Agric. Chem. **19:** 244 (May) 1936.

63. McFarlan, R. L.; Reddie, J. W., and Merrill, E. C.: A New Photoelectric Method for Measuring Vitamin A, Indust. & Engin. Chem. **29:** 324 (July 15) 1937.

as the inner "bleached" leaves, which make up the head. The outer green leaves of a head of young cabbage are much higher in vitamin A content than the inner white leaves.

Other types of green vegetables having a high vitamin A potency include green seeds and seed foods such as peas and green snap beans, fleshy vegetables such as green peppers, and green stems such as asparagus, broccoli stalks and green celery, although these products are not as rich as the green leaves. Here again there is loss of vitamin A value with loss in green color, since bleached celery stalks contain little, if any, of the vitamin.

In many plant products vitamin A activity may be indicated by the yellow color of the carotene. Of the vegetables the most notable examples are carrots and sweet potatoes, both of which are excellent sources. A yellow color is especially valuable in detecting fruits that contain vitamin A, such as apricots, yellow peaches and bananas. When there is a yellow and a white variety of a given species, the yellow variety invariably has a higher vitamin A value than the so-called white variety. For example, yellow peaches and yellow tomatoes are good sources, whereas the corresponding white varieties are fair or insignificant sources. A yellow color cannot be taken as an infallible guide to vitamin A activity, however, since there are yellow plant pigments other than carotene.

Seeds such as the cereal grains, nuts and legumes are, with the exception of those having considerable green and yellow color, poor sources of vitamin A. Yellow corn—corn with a yellow endosperm—is the most important vitamin A food in this group.

A red color is sometimes mentioned as a guide to vitamin A content. It is true that such foods as red tomatoes and red peppers may be good sources. In these particular cases, however, it must be recalled that these products were green before they were red. On the whole, the association of a red color with high vitamin A content is probably more fortuitous than significant and should not be taken as anything more than indicative.

Thus a green or yellow color in foods of plant origin has come to be associated with high vitamin A activity, a rich green color indicating perhaps a relatively higher value than a yellow color.

Of the foods of animal origin, eggs, whole milk and milk products are the important sources, eggs having a rating of excellent, whole milk good and milk products of good or excellent, according to the proportion of milk fat they contain. Milk, however, since it is consumed in fairly large quantities, may be a more important source than its rating on the basis of units of vitamin A per hundred grams would imply.

Normally the cow derives her vitamin A entirely from plant material and the hen largely from the same source. Both carotene and vitamin A are secreted in milk and eggs, although the proportion of carotene to vitamin A is usually small.

The animal body does not seem to be capable of synthesizing vitamin A or the precursor carotene but must depend on its food for the needed supply. It is only reasonable to expect, therefore, that the vitamin A activity of such products as milk and eggs would vary according to the quantity of vitamin A in the diet of the respective species. There is ample evidence indicating that these products may vary between wide limits. This variability is not as great, however, as might be the case if the body were not capable of storing large quantities of vitamin A which may be released gradually during periods of low vitamin A intake, such as the period of winter feeding. That there is a gradually diminishing output of vitamin A during such periods rather than a sharp drop has been shown by the studies made by Fraps and his co-workers.[64] On the other hand, when the intake is increased there is a sharp rise in output unless the body store has been unduly depleted.

The total quantity of vitamin A put into the egg or the milk is small compared with the total quantity ingested by the respective species. There also seems to be a maximum value beyond which the vitamin A potency of milk, at least, cannot be raised.[65] Under similar feeding conditions the butter fat from different breeds of cows shows the same vitamin A activity, although the ratio of carotene to vitamin A may vary from breed to breed.[66]

The relation between the color of the egg and the vitamin A content is often questioned, color referring to the yolk and not to the shell, since the latter is a breed characteristic and has nothing to do with nutritive value. In eggs available on the market at present, the color of the yolk is of little value as a basis for the judging of vitamin A potency. If the hen has derived her vitamin A supply from green feed or yellow corn, the yolks of the eggs will be deep yellow and rich in vitamin A. On the other hand, if the diet of the hen has contained cod liver oil and the hen has not had access to green or other pigmented food, the egg yolks may be light in color though rich in vitamin A.

Variability in the vitamin A content of milk and eggs from the standpoint of food value is perhaps not as serious a problem now as it might have been, since under present day feeding practices there is not such a wide seasonal variation in the vitamin A content of the diet of dairy cows and of poultry as existed formerly. Liver might also be included in a categorical list of foods rich in vitamin A, since it is one of the richest food sources. As Sherman [67] has pointed out, however, this product can hardly be considered an important source since its production is conditioned by the demand for other meat and therefore could not be increased to supply the quantity needed to make it a regular constituent of the diet.

A consideration of the importance of various untreated foods is a small part of the story of the food sources of any vitamin. A natural food may be a perfectly good source of a vitamin and yet before it comes to the table be subjected to such treatment that little or none of this factor is left. Vitamin A is less likely, perhaps, to be lost or inactivated during procedures of manufacture and preparation at home than some of the other vitamins, since it is fairly stable to heat and not appreciably soluble in water. It is destroyed, however, by oxidation, and foods that are heated for long periods show appreciable loss of vitamin

64. Fraps, G. S.; Copeland, O. C., and Treichler, R.: The Vitamin A Requirements of Dairy Cows, Bull. 495, Texas Agricultural Experiment Station, 1934. Sherwood, R. M., and Fraps, G. S.: The Amount of Vitamin A Potency Required by Hens for Egg Production, Bull. 493, Texas Agricultural Experiment Station, 1934.

65. Watson, S. J.; Bishop, Gerald, and Drummond, J. C.: The Relation of the Colour and Vitamin A Content of Butter to the Nature of the Ration Fed: I. Influence of the Ration on the Yellow Colour of the Butter, Biochem. J. **28**: 1076 (no. 3) 1934.

66. Wilbur, J. W.; Hilton, J. H., and Hauge, S. M.: The Vitamin A Activity of Butter Produced by Guernsey and Ayrshire Cows, J. Dairy Sc. **16**: 153, 1933. Moore, Thomas: Vitamin A and Carotene: IX. Notes on the Conversion of Carotene to Vitamin A in the Cow, Biochem. J. **26**: 1 (no. 1) 1932. Booth, R. G.; Kon, S. K., and Gillam, A. E.: The Relative Biological Efficiencies of the Vitamin A and Carotene of Butter, ibid. **28**: 2169 (no. 6) 1934. Watson, Bishop and Drummond.[65]

67. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 5, New York, The MacMillan Company, p. 366.

A potency. It is not affected at the temperature of boiling water, so that foods cooked by boiling retain their vitamin A potency well. Canned foods have practically the same vitamin A value as the corresponding fresh foods. Canned products that have been stored for as long as from nine months to a year and in some cases for even longer periods still retain a large portion of their vitamin A potency.

The storing of foods in the frozen state offers one of the best methods of retaining the maximum vitamin value. The vitamin A value of frozen foods is for all practical purposes the same as that of the fresh products; provided, of course, that this statement is construed to apply to the frozen product or the defrosted product immediately after defrosting, since there may be a rapid loss of vitamin A value if the defrosted food is allowed to stand.

Dried, or dehydrated, foods show considerable loss in vitamin A content due, undoubtedly, to oxidation of the vitamin during the drying process. Dried products may show a further loss during storage.

Most foods in their natural state that are susceptible of storage for any length of time may be stored as long as from nine months to a year without serious loss of vitamin A value, and any loss taking place is very gradual.

Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT. H. A. CARTER, Secretary.

HANOVIA ULTRA SHORT WAVE GENERATOR MODEL #2700 ACCEPTABLE

Manufacturer: Hanovia Chemical & Mfg. Co., Chestnut Street and N. J. R. R. Avenue, Newark, N. J.

This Hanovia Short Wave Heat Generator, Model #2700, is designed for medical and minor surgical procedures. Standard equipment with this semiportable unit includes cuff and induction coil electrodes and various surgical accessories. Sufficient current is provided, according to the firm, for the electrosurgical procedures requiring cutting, coagulating and desiccating currents. When packed for shipping, the unit weighs 145 pounds.

The machine has a two-tube circuit with a fixed wavelength of about 14 meters. The patient circuit is inductively coupled.

Fig. 1.—Hanovia ultra short wave generator, model 2700.

Two variable air-spaced condensers, one in each patient's terminal, are used for tuning this circuit. One control tunes the two branches of the patient's circuit simultaneously. The unit is so arranged that the operating voltages to the filament, plate and grid of the oscillating tubes can be adjusted to line voltage variations between 100 and 140 volts.

A serial switching arrangement is provided for the filament and plate circuits of the tubes. The current is consequently first applied to the filament and then the plate permitting the use of a foot-switch in the plate circuit only, which is preferable for surgical uses. To reduce radio interference to a minimum, a choke is used in series with the primary side of the transformer.

The input, when operating at full load, is approximately 700 watts. The output is approximately 350 watts as measured by means of a 110 volt incandescent lamp load, galvanometer and photronic light sensitive cell.

A voltmeter is provided on the panel to permit the operator to correct any fluctuations in line voltage, so that the electronic emission from the tubes can be kept constant under all operating conditions. A milliammeter is provided in the plate circuit of the tubes to indicate when resonance is obtained in the patient circuit. The oscillating circuits are so coupled that the maximum plate current reading corresponds to circuit resonance. The electrical characteristics are so designed, according to the firm, that it is impossible to overload the machine when using cuff or bare metal electrodes.

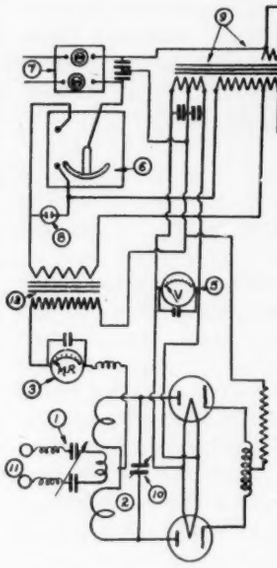

Fig. 2.—Schematic diagram of circuit.

The temperature rise of the transformer was found to come within the limits of safety. Burns may be caused by this machine as by any other short wave unit but are less likely to occur than when conventional diathermy is used and may be avoided by the use of ordinary precaution.

In order to substantiate heating claims made for this unit the firm supplied data collected from a number of observations. In making the tests, the procedure recommended by the Council on Physical Therapy was followed. A cannula was introduced at the midpoint of the thigh and inserted for a distance of two inches or until the bone was encountered. Temperature readings were made by means of thermocouples inserted into the cannula and constructed of constantan and copper placed in hypodermic needles. The constant junction was kept at 0 C. by means of a vacuum bottle and crushed ice. The couples were calibrated against a mercury thermometer certified and calibrated by the National Bureau of Standards. Potential differences were read from a Leeds and Northrup portable potentiometer of requisite sensitivity. The accuracy was believed to be within one tenth of a degree.

Six experiments were run with the cuff technic, either 3½ by 16 inches or 3½ by 21 inches. These were placed from 7 to 9 inches apart, center to center. They were spaced with felt varying from five-eighths to seven-eighths inches in thickness. The temperature averages are given here.

In using the coil technic, four turns were placed about the thigh, the outer turns in contact, the inner turns 3 inches apart.

Averages of Six Observations, Cuff Technic

Deep Muscle		Oral	
Initial	Final	Initial	Final
99.3	105.2	98.4	98.7

Averages of Six Observations, Coil Technic

Deep Muscle		Oral	
Initial	Final	Initial	Final
98.5	106.1	98.2	98.6

One layer of Zonas oiled silk was placed over the skin. Wooden air-spacers were used. The area treated was approximately 8 inches from top to bottom. In four of the tests the oiled silk was replaced by felt spacing, five-eighths inch thick.

The unit was tried out clinically by an investigator acceptable to the Council and rendered satisfactory service when used in conditions amenable to heat therapy.

In view of the foregoing report, the Council on Physical Therapy voted to accept the Hanovia Ultra Short Wave Generator, Model #2700, for inclusion in its list of accepted devices.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION

PAUL NICHOLAS LEECH, Secretary.

THIAMIN CHLORIDE.—Crystalline vitamin B_1 hydrochloride. — 3′-(methyl-4-aminohydrochloride-pyrimidyl-5-methyl)-N-4′-methyl-5′-beta-hydroxyethyl-3′-chlorothiazole. — $C_{12}H_{17}ClN_4OS.HCl$.

Thiamin chloride may be prepared from natural sources such as yeast or rice polishings and also synthetically.

Actions and Uses.—See general article vitamin B_1 (thiamin chloride), Allowable Claims, New and Nonofficial Remedies, 1938, page 471.

Dosage.—Dosage statements should be based on the minimum daily vitamin B_1 requirement of from 50 to 75 international units for infants and from 200 to 300 international units for adults.

Thiamin chloride occurs as white, nearly odorless crystals. On exposure to air, the crystals absorb water. It is very soluble in water, slightly soluble in alcohol. The aqueous solution (1:20) is acid to litmus (*pH* about 3.5). The absorption spectrum of thiamin chloride has two maximums, 233 millimicrons, 267 millimicrons and two minimums, 215 millimicrons, 250 millimicrons. Thiamin chloride decomposes on melting at 248-250 C. (micromelting point apparatus, rate of heating 5 degrees per minute). A solution of thiamin chloride in distilled water responds to the tests for chloride, U. S. P. XI, page 449.

Dissolve approximately 0.1 mg. of thiamin chloride crystals in 0.05 cc. of distilled water, or take 0.05 cc. of thiamin chloride solution (1 per cent) and add 0.05 cc. of 1 per cent solution of Reinecke Salt: immediately starlike, white crystals will appear.

Moisten 0.01 Gm. of thiamin chloride, accurately weighed, with 2 drops of sulfuric acid and ignite: no weighable residue remains. Test for heavy metals is negative (U. S. P. XI method). To 0.1 cc. of a 5 per cent aqueous solution of thiamin chloride, add 1 cc. of sodium hydroxide solution and heat gently: the escaping vapors do not turn moistened red litmus blue *(ammonium salts)*. To a solution of 0.01 Gm. of thiamin chloride in 2 cc. of distilled water, add 0.1 cc. of diluted hydrochloric acid and 0.1 cc. of barium chloride solution: no turbidity should develop in five minutes *(sulfate)*.

Dry 0.1 Gm. of thiamin chloride at 80 C. under reduced pressure (1 mm. mercury) to constant weight over phosphorus pentoxide (approximately ten hours): the loss in weight is not over 5.0 per cent. Dissolve about 0.02 Gm. of thiamin chloride, previously dried to constant weight and accurately weighed, in 2 cc. of water. Add 1 drop of phenolphthalein indicator solution and titrate with one-hundredth normal sodium hydroxide to a pink color: not less than 2.8 cc. nor more than 3.0 cc. of one-hundredth normal sodium hydroxide is consumed per 0.010 Gm. of thiamin chloride. Weigh out, accurately, about 0.05 Gm. of thiamin chloride, previously dried to constant weight, and determine the nitrogen by a modification of the micro Kjeldahl-Gunning-Arnold method, using selenium instead of mercury (Pregl-Quantitative Organic Microanalysis, second edition, P. Blakiston's Son & Co., 1930, p. 111). The nitrogen content is not less than 16.1 per cent nor more than 16.8 per cent. To about 15 mg. of thiamin chloride, previously dried to constant weight and accurately weighed, add 0.1 Gm. of potassium permanganate, 3 cc. of distilled water and 0.05 Gm. of sodium hydroxide. Heat the mixture for thirty minutes using a reflux condenser. Add sufficient hydrochloric acid, U. S. P. (not over 5 cc.), and heat until the solution is clear. Follow the Pregl method (Pregl-Quantitative Organic Microanalysis, second edition, p. 144) for finishing the determination of sulfur in the platinum-Neubauer micro crucible. The sulfur content is not below 9.20 per cent and not above 9.8 per cent.

For assaying tablets or ampule solution, dissolve the material in a measured amount of water and dilute so that the solution contains between 1 microgram and 5 micrograms of thiamin chloride in 1 cc. Transfer 0.2 cc. of the solution to a 25 cc. graduate cylinder and add 0.05 cc. of 1 per cent potassium ferricyanide solution and 3 cc. of 10 per cent sodium hydroxide solution. Shake the mixture and then let it stand for one hour, add 12 cc. of isobutyl alcohol and shake the mixture vigorously for two minutes. Let the mixture settle; filter 10 cc. into a 10 cc. graduate cylinder. Withdraw 4 cc. in a 25 mm. test tube and compare the solution under filtered ultraviolet light with standards of thiamin chloride. These standards are prepared by accurately weighing out previously dried thiamin chloride and diluting it until 1 cc. may contain from 0.1 to 5 micrograms per cubic centimeter. Transfer 0.2 cc. of these solutions to a suitable nonfluorescent test tube. Oxidize with potassium ferricyanide in alkaline solution, extract with isobutyl alcohol and compare 4 cc. of these standards with the unknown. The amount of the unknown solution is then calculated from the thiamin chloride standard solution matching the unknown. The potency of the tablets is also controlled by biologic assays.

Vitamin B_1 Hydrochloride (Thiamin Chloride)-Merck.—A brand of thiamin chloride-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J., under license from Research Corporation, New York. U. S. patents applied for.

McKESSON'S HALIBUT LIVER OIL PLAIN, 11 cc. (See New and Nonofficial Remedies, 1938, p. 496).

The following dosage form has been accepted:

McKesson's Cod and Halibut Liver Oil.—A blend of cod and halibut liver oils, adjusted to have the potency per gram of 2,100 U. S. P. units vitamin A and 210 U. S. P. units of vitamin D.

NUPERCAINE-CIBA (See New and Nonofficial Remedies, 1938, p. 69).

The following dosage forms have been accepted:

Ampules Solution of Nupercaine-Ciba, 1:1,500 in 0.5% solution of sodium chloride, 20 cc.

Ampules Solution of Nupercaine-Ciba, 1:1,000, with epinephrine, 1:100,000, 2 cc.

Ampules Solution of Nupercaine-Ciba, 1:1,000, with epinephrine, 1:100,000, 5 cc.

METYCAINE (See New and Nonofficial Remedies, 1938, p. 67).

The following dosage forms have been accepted:

Ampoules Solution Metycaine 10%, 2 cc.: Each 2 cc. contains metycaine 0.2 Gm. (3 grains) in distilled water. To be used for spinal anesthesia.

Ampoules Solution Metycaine 20%, 5 cc.: Each 5 cc. contains metycaine 1 Gm. (15½ grains) in distilled water. To be used for infiltration and regional anesthesia. The solution must be diluted before using.

NICOTINIC ACID AMIDE.—3: Pyridine Carboxylic Acid Amide.—The amide of nicotinic acid, $C_6H_6ON_2$.

Actions, Uses and Dosage.—Undetermined; the product is accepted for standardization and clinical experimentation only.

Nicotinic Acid Amide (3:Pyridine Carboxylic Acid Amide) SMACO.—A brand of nicotinic acid amide-N. N. R.

Manufactured by the S. M. A. Corporation, Cleveland. No U. S. patent or trademark.

Nicotinic acid amide occurs as fluffy, needle-like, white, odorless crystals with a slight bitter taste. The melting point is 133 C., when recrystallized from acetone. It is soluble in water, alcohol and hot benzene; only slightly soluble in ether.

Dissolve approximately 0.05 Gm. nicotinic acid amide in 5 cc. of hot water, add 0.05 Gm. of flavianic acid. Evaporate carefully to dryness and take up with 5 cc. of cold water. Centrifuge and wash the precipitate three times with 2.5 cc. portions of cold water. Recrystallize from 5 cc. of hot alcohol. Centrifuge and wash the crystals twice with 3 cc. portions of ether. Filter and dry the crystals: The melting point is found to be 269-270 C. (microscopic heating stage-heating time 30 degrees in one minute), $\alpha = 1.58$, $\beta = 1.70$, $\gamma = 1.8$.

Transfer 0.1 Gm. to a vessel and dry for five hours, at a reduced pressure 2 mm. of mercury in an Abderhalden dryer at 80 C. over phosphorus pentoxide: moisture content should not be more than 0.1 per cent. Incinerate 0.05 Gm. of nicotinic acid amide: no weighable residue remains. The test for halogens U. S. P. XI is negative. Weigh out, accurately, 5 mg. of nicotinic acid amide. Determine the nitrogen content after Pregl micro Dumas method: the nitrogen content should not be more than 23.2 per cent nor less than 22.6 per cent.

Council on Foods

THE COUNCIL ON FOODS HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.

FRANKLIN C. BING, Secretary.

GOLDEN WEST BRAND OLEOMARGARINE NOT ELIGIBLE FOR THE LIST OF ACCEPTED FOODS

The Cudahy Packing Company of Chicago presented its Golden West Brand of Margarine for consideration. The firm informed the Council that the product is manufactured in Los Angeles and that it is made from partially hydrogenated cottonseed oil, pasteurized cultured skimmed milk and salt (contains 0.1 per cent of sodium benzoate). The Council gave consideration to the evidence presented regarding the nature of the product and was of the opinion that, if the Rules and Regulations relative to labeling and advertising were met, the product would be acceptable. The package label for this brand of margarine bore a representation of tropical trees. It was the opinion of the Council that, in view of the fact that no descriptive statement of the product appeared on the label, the representation of the "palm" trees gave one the impression that the product was made from palm oil or coconut oil. Cottonseed oil is used in making the product and therefore this brand of margarine cannot be considered as a "nut" margarine. The firm was informed that it would be necessary to revise the label in such a way as to remove the Council's objection to it. This the firm was unwilling to do, stating that "the label was adopted some years ago because its design met with the approval of our advertising committee, and since its adoption it has become so well known among the trade that we are reluctant to make any alteration of it." The Council therefore has authorized publication of this statement that Golden West Brand of Margarine is not acceptable because the firm is unwilling to meet the requirements of the Council. In the opinion of the Council the product is satisfactory but the label is inappropriate.

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SATURDAY, JULY 16, 1938

DANGER OF PROTAMINE INSULINS

When the slow acting insulins were first employed clinically, it was hoped they would prove less toxic than the older insulin and that the possibility of developing hypoglycemia would be practically eliminated by their use. This hope has, however, not been fulfilled; reports of reactions have appeared in considerable number. Lawrence and Archer [1] in one of the earlier discussions of protamine zinc insulin said that hypoglycemia from this type is more subtle in onset and on the whole subjective symptoms are less severe than with soluble insulin. Preliminary symptoms of shakiness, sweating and palpitation may be absent; thus severe hypoglycemic symptoms may appear without warning. Four of their patients had this type of reaction.

Further attention was called to the caution necessary in the use of protamine insulin by Jordan.[2] An 11 year old girl received at 9 p. m. by accident double the usual dose of protamine insulin. About 3 a. m. she was found unconscious, delirious and thrashing about in bed. Although response was prompt to intravenous dextrose, the symptoms returned later and it was two days before a normal condition could be reestablished. More recently Lindsay [3] reported the case of a woman who had diabetes and cerebral arteriosclerosis. A short time following change of the insulin from the regular to the protamine type she was found comatose and she died soon thereafter. An analysis of the combined clinical and necropsy information led to the opinion that unconsciousness was due to prolonged and possibly severe hypoglycemia resulting from the cumulative effect of protamine insulin. It was concluded therefore that there is a definite possibility of danger to the arteriosclerotic patient from the prolonged and cumulative effect of the more complex insulin preparations.

Tolstoi [4] studied five cases of reaction to protamine zinc insulin and concluded that the hypoglycemia from protamine zinc insulin may appear from ten to twenty-four hours after its administration. Furthermore, reaction may be prolonged unless treated by epinephrine or intravenous medication. Moreover, insulin reactions of this type were often followed so rapidly by unconsciousness that little warning was available for either patient or attendants. In some of these cases, exercise appeared to be a contributing factor to the hypoglycemic reaction.

Attention has likewise been called to this modified insulin reaction by Joslin,[5] Mosenthal [6] and Kepler.[7] Margolin [8] has reported a case in which protamine insulin appeared to be at least one of the important contributing factors of death.

Ample evidence is therefore now available that protamine zinc insulin is not a fool-proof substitute for the older preparation. Although reactions to it seem to appear with less frequency, they also are often characterized by the suddenness of onset, delayed and therefore unexpected appearance, and symptoms precipitated by exercise at such a distant time as also to be wholly unexpected. Although the development of protamine zinc insulin is an advance of unquestioned value to many diabetic patients, the possibilities of delayed severe reactions cannot be ignored.

THE STANDARDIZATION OF LIVER PREPARATIONS

During the past year the U. S. P. Anti-Anemia Preparations Advisory Board has been engaged in the proper standardizing of official products. Several months ago physicians were informed that the potency of official liver products would hereafter be expressed in terms of units. The units are not interchangeable, depending on the mode of administration of the product.[1]

One of the new departures of the U. S. Pharmacopeia, Eleventh Revision, is the method of controlling liver preparations. This official compendium provides that:

1. There shall have been submitted, from time to time, as requested by the Board, satisfactory clinical data from treatment with the product in question, of cases of addisonian pernicious anemia.

2. The clinical data submitted shall satisfy the U. S. P. Anti-Anemia Preparations Advisory Board that the administration of the material in question, as prepared from liver or stomach, can produce a satisfactory result in the dose given.

1. Lawrence, R. D., and Archer, Nora: Zinc Protamine Insulin, Brit. M. J. **1**: 487 (March 6) 1937.
2. Jordan, W. R.: Caution in the Use of Protamine Insulin, Virginia M. Month. **63**: 730 (March) 1937.
3. Lindsay, J. W.; Rice, E. C.; Selinger, M. A., and Mish, K. H.: Protamine Insulin as a Contributing Factor in the Death of a Diabetic Patient with Cerebral Arteriosclerosis, Ann. Int. Med. **10**: 1892 (June) 1937.
4. Tolstoi, Edward: Protamine Zinc Insulin, New York State J. Med. **37**: 1279 (July) 15) 1937.
5. Joslin, E. P.: Protamine Insulin, J. A. M. A. **109**: 497 (Aug. 14) 1937; Difficulties in the Use of Protamine Zinc Insulin, ibid. **110**: 90 (Jan. 8) 1938. Joslin, E. P.; Root, H. F.; White, Priscilla; Marble, Alexander, and Joslin, A. P.: Protamine (Zinc) Insulin, M. Clin. North America **22**: 711 (May) 1938.
6. Mosenthal, H. O.: Protamine Zinc Insulin, J. A. M. A. **110**: 87 (Jan. 8) 1938.
7. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, J. A. M. A. **110**: 92 (Jan. 8) 1938.
8. Margolin, Morris: Protamine Insulin in the Treatment of Diabetes Mellitus, Nebraska M. J. **23**: 92 (March) 1938.
1. Report on Potency of Liver Products, J. A. M. A. **110**: 812 (March 12) 1938.

The Council on Pharmacy and Chemistry continues to accept liver products according to the criteria outlined in New and Nonofficial Remedies. In its minutes (published in THE JOURNAL July 9) the Council expresses the desire that the U. S. P. Anti-Anemia Preparations Advisory Board publish a statement of its standards. Since the meeting of the Council last March the Anti-Anemia Preparations Advisory Board has taken several important actions of interest to the medical profession. It has agreed that the board should publish the therapeutic and pharmacologic evidence which constitutes the basic factors for evaluating antianemia products. By so doing the board believes that the manufacturers will have a better idea of the meaning of the term "U. S. P. unit," and, secondly, that the standards agreed on will serve the board itself as a basis of comparison in determining the relative value of the submitted products. In taking this action, however, the board points out that such data are only a part of the criteria considered to determine the potency of a product, and the board reserves the right to use its own judgment and reach its own decisions based on all evidence presented. It is presumed by this that the board feels that the competence of the individual furnishing the data is of equal importance with the data themselves.

No sooner had the matter of expressing potency in terms of units been announced when commercial interests began either to increase the potency of their products in a competitive effort or, in case of certain nonaccepted preparations, to create units of their own. The board has decided not to grant U. S. P. recognition to injectable products of a greater potency than 15 units per cubic centimeter. As the exact composition of the active principle in liver extracts is not known chemically, the board feels that in the race to concentrate the material to a higher potency some valuable ingredients may be eliminated in the process of concentration. It is hoped that the profession will not be subjected to varying definitions for the unit of potency.

Another equally important decision is that which follows the reasoning of the Council on Pharmacy and Chemistry. The board has decided not to give consideration for acceptance or evaluation of any unofficial mixtures of antianemia products with vitamins, iron or other therapeutic agents. This is decidedly in the interest of rational medicine. When new products, such as liver and sulfanilamide, are introduced to the profession, some pharmaceutical houses immediately endeavor to complicate the therapy by presenting the physician with ready-made mixtures. If other drugs are indicated (and they frequently are not indicated), the physician should be permitted to prescribe them concurrently and in the ratio indicated for the particular patient; in other words, to use individualized medication. The board wisely points out that, without definite clinical evidence of the value of combinations of products with liver, and with some indication that the antianemia factor may deteriorate by the addition of some of these compounds, it is desirable to avoid all these mixtures and to administer antianemia preparations separately.

Finally, the board has decided that it will not approve the use of the statement that the liver extract used in compounding a mixture has a certain number of U. S. P. units, because the action of the vitamin or other added product on the liver extract is not known. Only when products are tested in final form and without vitiating influence can their value be assigned.

MEDICAL EXAMINATIONS FOR DOMESTICS

Experienced physicians have occasionally encountered cases of infectious disease contracted from domestic servants. Attention was called specifically to this public health problem in the May issue of *Hygeia*.[1] Although it is feasible for prospective employers to insist on medical examination, it seems questionable that this method will have sufficiently widespread adoption to be effective. In a paper read before the International Health Officers' Conference last year, Dr. M. J. Exner [2] of the Health Department of Newark, N. J., described the experiences in that city with the obligatory medical examination of domestic employees in force since September 1930. By the ordinance passed at that time every domestic was required to file with the department of health a certificate from a duly licensed physician stating freedom from contagious and communicable disease. Until 1934 the examination consisted only of inspection of the skin, examination of the mouth, throat and eyes, swabs for smears only in the presence of a discharge, blood tests only with a history of typhoid or syphilis, vaccination when no scar was evident, physical examination of the chest, and x-ray or fluoroscopic examination when abnormal conditions were found. Since early in 1934 blood tests for syphilis have been made in all cases and cervical smears have been examined in all women; in men a routine inspection of the generative organs has been made and smears have been examined in event of any discharge. If the applicant was found free from infectious states, a health card was issued good for six months. If tuberculosis or syphilis was found not in the infectious state, the health cards were issued subject to being revoked if the patient failed to continue treatment.

Since June 1, 1934, the Newark Department of Health has made more than 24,000 examinations of domestics. These have shown a syphilis rate of 17.1 per cent (4.7 among white patients and 26 per cent among Negroes) and a rate of 2.4 per cent of gonorrhea. The results,

1. Kruglick, J. S.: The Real Servant Problem, Hygeia **16**: 400 (May) 1938.
2. Exner, M. J.: The Medical Examination of Domestics, read before the International Health Officers' Conference in 1937.

however, are not an exact measure of the prevalence of syphilis because they include reexaminations; but since infectious and noninfectious persons reappear with approximately equal frequency, the prevalence rate is not widely divergent.

The argument for examinations of this nature is threefold: the protection of the family of the employer and the general public, the protection and welfare of the domestics themselves, and the general influence on disease control. Furthermore, as pointed out by Exner, the addition of large occupational groups of the general population to satisfactory syphilis control measures in the infectious stage probably serves as the best means of eradicating this controllable disease. The advantages of a comprehensive program for the examination of domestics to all groups concerned are such as to commend this activity to the serious attention of local medical societies, health departments and governmental agencies.

RENAL RICKETS

Renal rickets, renal pseudorickets, renal dwarfism and renal infantilism are terms variously employed to designate a syndrome characterized by the combination of chronic renal disease and deformity of the bones. In 1870 Steiner and Neureutter reported finding six cases of granular atrophic kidney among 256 cases of nephritis in children in which necropsies were performed. Lucas in 1882 reported five cases in which late rickets was associated with albuminuria. He considered the cases to be true rickets and suggested for them the term "rickets of adolescence." More recent investigators, particularly Fletcher and Parsons, have recognized the etiologic relationship between chronic kidney disease and deformities of the bones. In 1930 Mitchell [1] collected from the literature reports of seventy-six cases of renal rickets, to which he added two.

The symptomatology of this unusual condition is essentially that of nephrosclerosis associated with deformities of bone resembling true rickets. The sex distribution is about even. The average age of the onset is 7 years, but symptoms may manifest themselves in early infancy. In the presence of a normal mentality there is a stunted growth and failure or retardation of sex development at puberty. Among the early symptoms are anorexia, headache, vomiting, polyuria and polydipsia. Albuminuric retinitis is frequent and anemia is a constant symptom. Urinalysis shows low specific gravity, albumin, an occasional hyaline cast, and red and white cells. Kidney function tests reveal severe renal insufficiency. Increase in blood pressure is a late sign. Pigmentation of the skin described as sallow, brownish, grayish green or bronzing is a somewhat characteristic sign. Knock knees, the most constant sign, may be the first symptom which calls attention to the underlying condition.

The changes in the kidneys in the majority of cases of renal rickets are typical of granular atrophy or chronic interstitial nephritis; other pathologic conditions such as urinary calculi have been recorded. These apparently lead to kidney dysfunction and functional insufficiency, obstruction of the urinary tract, congenital dilatation of the urinary passages, acquired or postnatal urinary obstruction and congenital cystic kidney.

The changes in the bones resemble grossly those in true infantile rickets. Enlargement of the epiphyses of the wrist and costochondral junctions, pigeon shaped chest, bossing of the frontal and parietal bones and deformities may occur. Roentgenologic and histologic studies, however, demonstrate that these alterations are somewhat different from those seen in infantile rickets; the shafts of the long bones and the flat bones have greater translucence and a more spongy appearance than are usually seen in ordinary rickets. Parsons [2] in roentgenologic studies of renal rickets described three well defined groups: (1) the atrophic type, (2) the florid type, which is much like that of florid rickets, and (3) the woolly, stippled or honeycombed type, which appears to be characteristic for renal rickets and quite unlike the appearance associated with true rickets.

It is assumed that the condition is a primary kidney complex resulting in faulty deposition of minerals in osseous tissues. That nephritis does occur in fetal life and in infants has been established at necropsy. Heredity and acute infections, particularly those of streptococcic nature, are among the known etiologic factors. Blood chemistry studies in renal rickets revealed a reversal of the relation between the calcium and the inorganic phosphorus content; during the acute stage, serum calcium is at its lower normal limit while the inorganic phosphorus is at its upper limit. It differs from true infantile rickets in the absence of proof that lack of minerals in the diet is concerned in the pathogenesis of the bone changes; furthermore, the antirachitic factor and ultraviolet rays do not influence renal rickets favorably. It is believed that the cause of the diminished deposition of calcium in the bone is the inability of the kidney to excrete phosphate, which leads to elevation of the blood phosphorus and depression of blood calcium. Mitchell offers the hypothesis that in renal rickets there is a shift of the excretion of the endogenous phosphates from the kidney to the intestine. He suggests that these waste phosphates will be largely in the form of sodium phosphates and ammonium phosphates, forms suited for precipitation of calcium in the intestine. The absorption of calcium will be interfered with presumably because of the formation of insoluble calcium phosphate. Blocking by the phosphorus of the absorption of calcium from the food would then lead to true calcium starvation.

1. Mitchell, A. Graeme: Nephrosclerosis in Childhood, with Special Reference to Renal Rickets, Am. J. Dis. Child. **40**: 101 (July), 345 (Aug.) 1930.

2. Parsons, L. G.: The Bone Changes Occurring in Renal and Celiac Infantilism and Their Relationship to Rickets, Arch. Dis. Childhood **2**: 1 (Feb.) 1927.

The prognosis is bad. The patients die of uremia as a rule in the second decade. Howard [3] suggests the possibility of preventing a fatal termination by the early recognition and correction of obstructive pathologic conditions in the urinary tract in some cases. He reports a case in which removal of obstruction to the neck of the bladder resulted in restoration to health.

Current Comment

WHAT IS ADEQUATE HOSPITAL SERVICE?

In the United States, for a population of a hundred and twenty million people, there are 1,124,548 hospital beds, or a ratio of 9.3 hospital beds per thousand people. Excluding mental hospitals, the figure is 4.6. Such ratios, however, when taken alone do not suffice to answer the question as to whether or not we have adequate hospital service. Much depends on whether the population is rural or urban, on the type of housing which prevails, on the availability of servants, on the habits of the people and on the degree to which they have become accustomed to the idea of hospitalization for minor illnesses. In 1937 those states which had the highest percentage of occupancy were the states which had the highest bed ratio, while the states with the smallest number of hospital beds in relation to the population had the largest percentage of unoccupied beds. This would seem to indicate that hospitals have been built where they were needed and have not been built where they are not needed. Another method of appraising the adequacy of hospital service is based on geographic distribution. On the following page of this issue of THE JOURNAL is a map of the United States which shows in white all those areas which are within thirty miles of a registered hospital; the remainder of the country is shown on the map in black. It is obvious that the black areas are chiefly confined to the Rocky Mountain areas and adjacent territory. In the United States 98.5 per cent of the people live within thirty miles of a hospital.

MATERNAL AGE AND MONGOLISM

In spite of the antiquity of mongolism as a medical subject, its causation has remained obscure. Bleyer [1] has recently analyzed its incidence in relation to advanced maternal age, low fecundity among women bearing children with mongolism, prolonged interval preceding the birth of a mongoloid imbecile, maternal reproductive exhaustion, ultimogeniture and paternal reproductive exhaustion. He concluded from these studies that the role of advanced maternal age in causing mongolism is undeniable. Although the peak maternal age in the general population in this country in 1934 was 24, the peak age of mothers producing mongoloids in his series of 2,822 cases was 41. Furthermore, the incidence of mongolism increases steadily through the child-bearing period. The likelihood of producing a mongoloid imbecile is increased in direct proportion to the number of menstrual cycles through which a woman has passed. Of the entire group of 2,822 mongoloid imbeciles, 900 were born to women under 31 years of age and 1,922 to women over 31. Mothers from 15 to 19 years of age produced 3.4 per cent of the mongoloid imbeciles, or only one-fourth the expectancy when judged by their proportionate contribution to the total births. In the years from 35 to 39, the mothers producing only 0.9 per cent of the births in the general population gave birth to 23.8 per cent of the mongoloid imbeciles, or an excess over expectancy of 25 to 1. The succeeding five year period, from 40 to 44, showed a further increase above expectancy of 75 to 1. No satisfactory evidence could be found of the relationship to the etiology of mongolism of the other factors investigated. Probably the apparent relation of any of these factors to mongolism can be explained simply through the admixture of advanced maternal age.

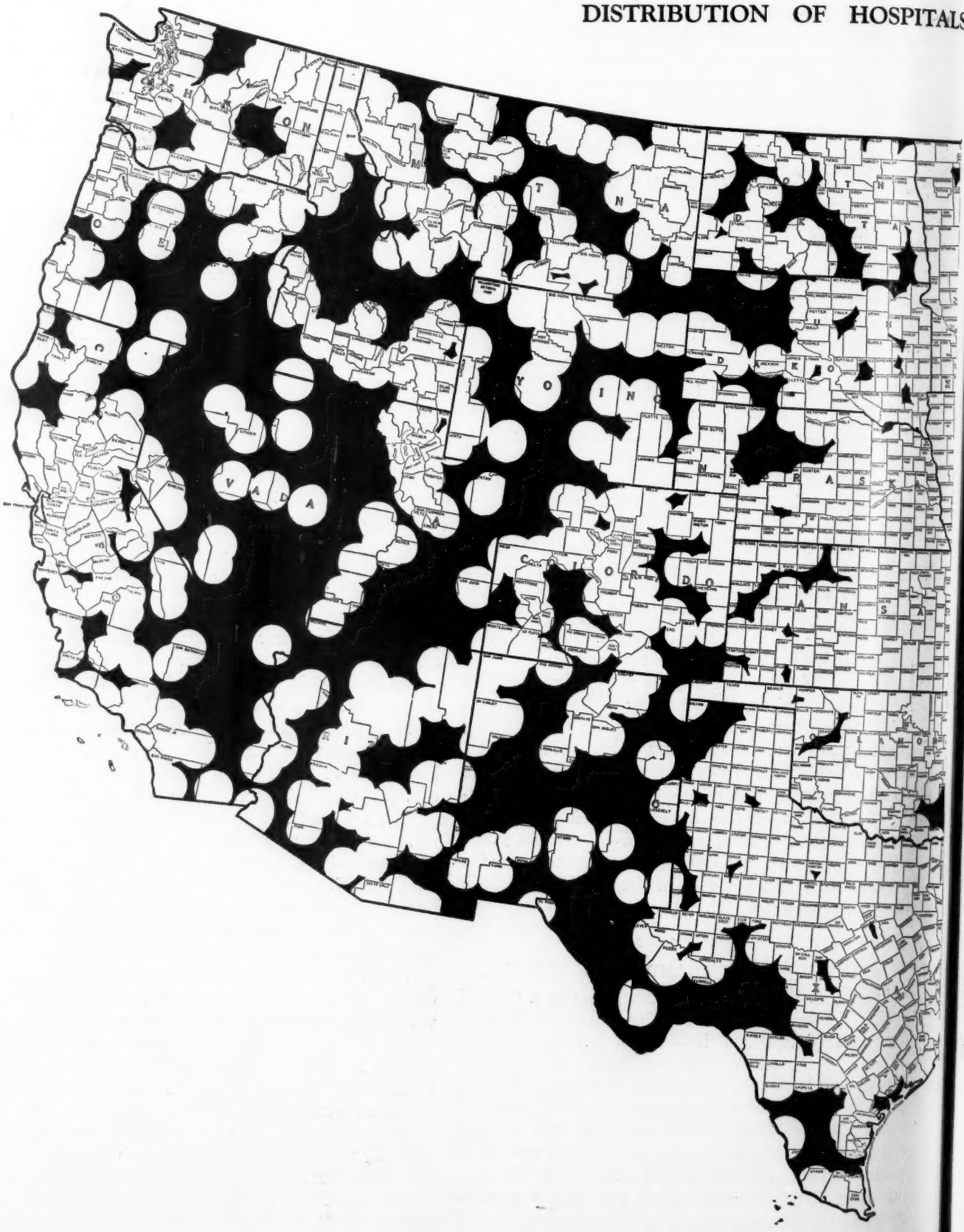
3. Howard, T. L.: Renal Rickets or Renal Dwarfism, Am. J. Surg. **40**: 323 (May) 1938.

1. Bleyer, Adrien: Role of Advanced Maternal Age in Causing Mongolism, Am. J. Dis. Child. **55**: 79 (Jan.) 1938.

VITAMIN B DEFICIENCY AND PEDICULOSIS

Among the curiosities of current pathologic research is György's [1] recent observation that vitamin B_2 deficiency is often associated with pediculosis in rats and that avitaminotic lice-infested rats can be successfully deloused by the oral administration of riboflavin. If confirmed, this observation would seem to suggest that riboflavin is a necessary factor in the normal sensory acuity of the skin, a deficiency in this factor reducing skin sensitivity so that the rats do not keep themselves normally free from these parasites. Other explanations are, of course, possible. György's observation was a by-product of a five years study of the various types of vitamin B deficiency. Pediculosis was observed in about 20 per cent of all rats that were kept for from two to three months on a vitamin B_2-free diet. Lice, however, did not appear in control rats fed diets free from other fractions of the vitamin B complex. Therapeutic administration of riboflavin to the lice-infested rats was followed by a complete disappearance of the parasites, often accompanied by replacement of diseased patches by new fur. At first György regarded this phenomenon as purely coincidental, probably associated with a generally diminished vitality of the rats, which might then be unable to keep themselves clean in the efficient manner of normal animals. To his surprise, however, the majority of the lice-infested rats were by no means weakened or inactive. Moreover, pediculosis was not observed even in moribund rats suffering from B_6 avitaminosis or in rats moribund for lack of the maturation factor. He therefore concluded that the observed pediculosis was specific for riboflavin deficiency. Effects of B_2 avitaminosis on cutaneous reflexes and sensory acuity have not yet been studied, nor have the conceivable changes in the odor, flavor or p_H of the skin as yet been investigated.

1. György, Paul: Proc. Soc. Exper. Biol. & Med. **38**: 383 (April) 1938.



Map of United States, showing in WHITE all areas within 30 miles of a hospital, and in BLACK all areas not

IN THE UNITED STATES

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within 30 miles of a hospital; 98.5 per cent of the population of the United States lives within 30 miles of a hospital.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ALABAMA

Personal.—Dr. Alfred G. Rice, Northville, Mich., has been appointed director of tuberculosis control in North Alabama, succeeding Dr. Kellie N. Joseph, Birmingham, who retired to reenter private practice.

Society News.—At a joint meeting of the northern divisions of the Medical Association of the State of Alabama in Clarence, June 2, the speakers included Drs. Arthur B. Harris, Birmingham, on "Glioma of the Retina"; William B. Anderson, Nashville, Tenn., "Chronic Bright's Disease in Pregnancy"; Cecil D. Gaston, Birmingham, "The Enema"; James O. Morgan, Gadsden, "Uteroplacental Apoplexy" and Carl A. Grote, Huntsville, "Heart Disease and Its Treatment in General Practice."

CALIFORNIA

Plague Infection in Santa Cruz County.—According to *Public Health Reports*, plague infection was proved in fleas collected from beecheyi squirrels in Santa Cruz County as follows: A pool of six lots of fleas from ranches in the vicinity of Watsonville, which produced typical plague when inoculated into guinea pigs April 27; seventeen fleas from two beecheyi squirrels collected April 27, 8 miles east of Watsonville, and sixty fleas from one beecheyi squirrel, found dead 6 miles east of Watsonville. According to the state department of health, May 11, infection had been proved in eighteen fleas collected at the mouth of a squirrel burrow in Santa Cruz County.

Dr. Warnshuis Goes to Massachusetts.—Dr. Frederick C. Warnshuis, San Francisco, formerly secretary of the California Medical Association, has been appointed president of the American Medico-Legal Association with headquarters in Boston and editor-in-chief of its journal. The association, which was chartered in Massachusetts nine months ago under the sponsorship of some Eastern medical men, attorneys and educators, aims to coordinate all branches of the medical profession and to seek uniformity in rules and regulations dealing with medico-legal work. Its journal will be devoted to medical jurisprudence, and will be published bimonthly with eighty or more pages per issue. The first issue is expected to appear in September. Present members of the editorial board include:

Dr. George B. Magrath, emeritus professor of legal medicine, Harvard University Medical School, Boston.
Eugene O'Dunne, judge of the supreme court in Baltimore, lecturer in medical jurisprudence, Johns Hopkins University.
Dr. Tracy J. Putnam, professor of neurology, Harvard.
Dr. Myrtelle M. Canavan, curator, Warren Anatomical Museum at Harvard.

Archers Honor Dr. Saxton Pope.—The memory of Dr. Saxton T. Pope, for many years a member of the teaching faculty in the department of surgery of the University of California Medical School, San Francisco, was honored by archers of the United States July 3 when ceremonies were held the first day of the annual championship tournament of the Western Archery Association on the campus of the university at Los Angeles. Dr. Pope is credited with making archery popular in this country. According to the "History of the California Academy of Medicine," Dr. Pope's interest in the use of the bow and arrow as a sporting weapon dates from 1912 when he met Ishi, the sole survivor of the Yana tribe of Indians. He wrote "A Study of Bows and Arrows" and "The Medical History of Ishi." From 1912 until 1925 there were about seventeen expeditions made to hunt solely with the bow and arrow. In 1925, the last of the expeditions, Dr. Pope went to Africa in the company of Stewart Edward White and his companion Arthur Young. Just prior to his death, Aug. 8, 1926, from pneumonia, Dr. Pope wrote the story of the expedition in the book "The Adventurous Bowman." Born in Texas Sept. 4, 1875, Dr. Pope served as secretary of the San Francisco County Medical Society and in 1922 as president; he was director of the League for the Conservation of Public Health and secretary of the California Academy of Medicine, 1913-1914. He graduated at the University of California Medical School in 1899, becoming a member of its faculty in 1912 after carrying on a surgical practice in Watsonville.

COLORADO

Society News.—Dr. Harry H. Wear, Denver, addressed the Montrose County Medical Society May 6 on "Urologic Problems of the General Practitioner."——At a meeting of the Crowley County Medical Society May 6 Dr. William T. H. Baker, Pueblo, spoke on medical economics.——Drs. Alexander D. Waroshill and Royal C. Adkinson, Florence, discussed cholecystitis and cholelithiasis before the Fremont County Medical Society.——Drs. Samuel P. Newman Jr. and Alfred M. Wolfe, Denver, discussed "Fractures of the Elbow and Ankle" before the Northeast Colorado Medical Society at its meeting in Sterling May 12.——Dr. Alta E. C. Bordner, Pueblo, discussed marihuana before the Pueblo County Medical Society May 17.

CONNECTICUT

Personal.—Dr. Alice Hamilton, Hadlyme, received the honorary degree of doctor of science from the University of Rochester (N. Y.) at its eighty-eighth annual commencement June 20.——Dr. De C. Y. Moore, chairman of the board of health and health officer of Manchester for nearly twenty-five years, has been appointed medical examiner to succeed the late Dr. Le Verne Holmes.

DISTRICT OF COLUMBIA

Society News.—Dr. Winfred Overholser addressed the Academy of Medicine of Washington at its spring meeting May 14 on "The Psychiatrist in Court."——Dr. Daniel L. Borden has been elected president of the Washington Academy of Surgery and Dr. John O. Warfield Jr. secretary.

Survey of Cancer of Lungs.—The U. S. Public Health Service is conducting a survey of cancer of the lungs in Washington hospitals as a part of a national study, according to the Washington *Star* June 7. Dr. James A. Crabtree, Chattanooga, Tenn., formerly assistant head of the health and safety department of the Tennessee Valley Authority, is in charge. Similar studies will be made in hospitals throughout the country treating cancer.

ILLINOIS

New Health District.—Dr. Wilmier M. Talbert, Decatur, formerly city physician for Decatur, has been appointed health officer of a new district health unit with headquarters at Clinton. The counties of Macon, Moultrie, Dewitt, Piatt and McLean are included in the new unit.

Chicago

Graduate Course in Pediatrics and Obstetrics.—A graduate course in obstetrics and pediatrics will be conducted by the department of obstetrics and pediatrics at Research and Educational Hospital during July and August. The speakers will include Drs. Joseph L. Baer, Frederick H. Falls, Fred L. Adair, William C. Danforth, Abraham F. Lash, William H. Browne and Charles Newberger, all obstetricians, and Drs. Julius H. Hess, Clifford Grulee, Arthur H. Parmelee, Isaac A. Abt, Maurice L. Blatt, Robert A. Black and Henry E. Irish, all pediatricians. The course, consisting of lectures on special subjects, round table discussions, ward walks in the hospital, dispensary service, manikin, home and hospital delivery, is designed to meet the needs of the general practitioner as they are encountered in everyday practice. The registration fee is ten dollars; checks should be made payable to the University of Illinois, 1853 West Polk Street.

INDIANA

Survey of Industrial Hazards.—A study of industrial hazards will begin this month in Indiana, according to the state medical journal. Conducted by the new bureau of industrial hygiene, the survey is expected to provide a cross section of health conditions in the state's factories. While it will not be possible to inspect every plant, a check will be made in industries known to have hazardous health conditions.

Society News.—Dr. John W. Ferrin, Chicago, discussed prostatic surgery before the LaPorte County Medical Society in Wanatah May 19.——The Daviess-Martin County Medical Society was addressed in Washington May 31 by Dr. William N. Wishard Jr., Indianapolis, on "Prostatic Obstruction."——Dr. Emor L. Cartwright, Fort Wayne, discussed diseases of the rectum and anus before the Adams County Medical Society in Decatur May 20.——At a meeting of the Parke-Vermillion County Medical Society in Clinton May 18 Dr. James H. Hawk, Indianapolis, spoke on puerperal infection and antepartum care.——The Wayne-Union Counties Medical Society was addressed in Liberty June 9 by Dr. Franklin D. Johnston, Ann Arbor, on

"Electrocardiology in Diagnosis of Coronary Occlusion."——Dr. Frank H. Lahey, Boston, discussed "Peptic Ulcer: Its Nonsurgical and Surgical Management" before the Muncie Academy of Medicine May 10.

IOWA

District Meeting.—The Iowa and Illinois Central District Medical Association held its annual meeting at the Outing Club in Davenport May 25. The speakers were Drs. Dallas B. Phemister, Chicago, on "Use of the Bone Graft in the Treatment of Bone Tumors"; Alexander E. Brown, Rochester, Minn., "Sulfanilamide Therapy," and James H. Means, Boston, "The Commoner Deficiency Syndromes Found in a Medical Clinic." Dr. Anton Knutson, Reynolds, Ill., lectured in the evening on "Hunting Big Game in Africa." Two members who have completed fifty years in practice were given special recognition at this meeting: Drs. George B. Maxwell, Davenport, and George A. Wiggins, Milan, Ill.

KANSAS

Hall of **Health in Wichita.**—The Sedgwick County Medical Society sponsored a "hall of health" in Wichita May 7-16. The period of the exhibit included the annual session of the Kansas Medical Society. It was formally opened with the unveiling of the Camp Transparent Woman, the ceremony being broadcast over a local radio station. There was a 10 cent admission charge; the cost was $2,500 and a total of 27,000 persons visited the hall. The society furnished the rent, booth space, shelving and electricity free of charge. There were fifty-two exhibit spaces.

KENTUCKY

Society News.—Drs. Dougal M. Dollar and John Stites addressed the Jefferson County Medical Society, Louisville, June 6, on "Anesthesia" and "Agranulocytosis" respectively. At the meeting June 20 the speakers were Drs. Gordon S. Buttorff, "Control of Hemorrhage with Special Reference to Moccasin Snake Venom"; Ellis S. Allen, "Hazards of Blood Transfusion," and William J. Martin, "Anal Fissure."——Dr. George A. Hendon addressed the Louisville Surgical Society June 3 on "Multiple Abscess of the Liver."——Dr. Frederick G. Speidel addressed the Society of Physicians and Surgeons of Louisville June 16 on "Treatment of Nephritis."——Dr. John Walker Moore, Louisville, addressed the Louisville Medico-Chirurgical Society recently on "Studies in Hemodynamics of Patients Receiving Insulin Shock Therapy."——Drs. Franklin H. Russell, Wickliffe, and Willis R. Moss, Clinton, addressed the Tri-County Medical Society of Hickman, Carlisle and Ballard counties June 7 on angina pectoris and scarlet fever, respectively.

LOUISIANA

Past Presidents' Night.—The Orleans Parish Medical Society devoted its June 29 meeting to honoring past presidents. Dr. Shirley C. Lyons gave the address of welcome and Dr. Marcus J. Magruder the response. Dr. James M. Mason, Birmingham, Ala., gave "A Review of Progress in the Treatment of Empyema" and Dr. Rudolph Matas presented certificates to the honor guests on behalf of the society. There have been forty-eight presidents since 1878, when the society was established.

MASSACHUSETTS

Personal.—Dr. Ruth E. Fairbank, associate in psychiatry, Johns Hopkins University School of Medicine, Baltimore, has been appointed professor of hygiene at Mount Holyoke College, South Hadley, *Science* reports. Dr. Fairbank graduated at Johns Hopkins in 1916.

Courses for Graduates.—A course in urology will be held at the Harvard University Medical School, Boston, July 18-30, under the direction of Dr. George G. Smith and his associates. Mornings will be devoted to operations, ward visits, cystoscopic diagnosis of urologic problems, while the afternoons will be given over to special discussions. The fee is $80. Additional information may be obtained from the assistant dean, Courses for Graduates, Harvard University Medical School, Boston.

MICHIGAN

Society News.—Dr. John J. Prendergast Jr., Detroit, has been elected president of the newly organized Michigan Society for Industrial Hygiene.——Dr. Harold L. Morris, Detroit, discussed "Pyelitis of Pregnancy" before the Muskegon County Medical Society in Muskegon June 17.

MINNESOTA

Dr. Harrington Honored.—A dinner was given for Dr. Francis E. Harrington, health commissioner of Minneapolis and founder and director of the Lymanhurst Health Center at the Minnesota Union, University of Minnesota, May 23. The occasion also commemorated the seventeenth anniversary of the health center as a school for tuberculous children. Dr. William A. O'Brien, associate professor of pathology and preventive medicine and public health, University of Minnesota Medical School, Minneapolis, was toastmaster and speakers included Drs. Arthur E. Benjamin, Stephen H. Baxter, Chester A. Stewart, Jay Arthur Myers and Irvine McQuarrie, all of Minneapolis; Robert B. J. Schoch, health officer of St. Paul, and Carl Buck, Dr.P.H., New York, field director of the American Public Health Association.

Dr. Meyerding Resigns—Receives Award.—Dr. Edward A. Meyerding, St. Paul, secretary of the Minnesota State Medical Association for fourteen years, resigned at the recent annual meeting in Duluth. Dr. Meyerding had been on a year's leave of absence from the association. He will continue on a full time basis as executive secretary of the Minnesota Public Health Association, a position he has also held since 1924. At the annual banquet of the association June 30, Dr. Meyerding was presented with the first Distinguished Service Award created by the house of delegates of the state society to be presented on occasion in recognition of special service to the association. A native of St. Paul, Dr. Meyerding graduated at the University of Minnesota Medical School, Minneapolis, in 1902. Before he became associated with the medical and public health associations, he served as director of the division of hygiene and special classes of the public schools of St. Paul for fifteen years. He is president of the Mississippi Valley Conference on Tuberculosis.

MISSOURI

Annual Fall Conference.—The sixteenth annual fall clinical conference of the Kansas City Southwest Clinical Society will be held in Kansas City, October 3-6. Guest speakers will include Drs. Grady E. Clay, Atlanta, Ga.; James B. Costen, St. Louis; Thomas Leon Howard, Denver; Chester A. Stewart, Minneapolis; William J. Dieckmann, Chicago; Frank R. Ober, Boston, Mass.; Louis J. Karnosh, Cleveland; Elmer L. Sevringhaus, Madison, Wis.; William D. Sansum, Santa Barbara, Calif.; Lawrence Reynolds, Detroit, and Isidor S. Ravdin, Philadelphia.

Cornerstone Laid for Psychopathic Institute.—The cornerstone of the new Malcolm A. Bliss Psychopathic Institute, St. Louis, was laid June 26. A city institution, the building will cost about $1,000,000 and accommodate 185 patients, with 142 beds for white patients and forty-three for Negroes. Funds for the project came from a 1934 bond issue and a PWA grant, newspapers reported. The institute will be primarily for the study of new and borderline cases, the latter to be segregated from the actually insane. The building will be ready about March 1939. Dr. Bliss, in whose honor it is named, was for many years associated with the city institutions. He died in 1934.

NEW HAMPSHIRE

Shellfish from Bay Area Banned.—The state board of health has recently placed a ban on the sale for human food of shellfish taken from the "Great Bay area" because of contamination of rivers flowing into the area with sewage from Portsmouth, Dover and other towns. Collection and analyses of clams and water from the lower part of the area has definitely shown that shellfish taken there is unfit for food, and studies are in progress of clams from the mouth of the Exeter River and oysters from the Oyster River.

NEW JERSEY

Dr. Shope Awarded Alvarenga Prize.—The College of Physicians of Philadelphia has awarded the Alvarenga Prize for 1938 to Dr. Richard Edwin Shope of the department of animal and plant pathology of the Rockefeller Institute for Medical Research, Princeton. The award was made in recognition of his research on influenza. Dr. Shope, who is 35 years old, is a graduate of the State University of Iowa College of Medicine, Iowa City, and has been associated with the Rockefeller Institute since 1925. In 1937 he received the John Phillips Memorial Prize of the American College of Physicians. The Alvarenga Prize was established by the will of Pedro Francisco deCosta Alvarenga, an associate fellow of the College of

Physicians of Philadelphia, to be awarded annually on the anniversary of the death of the donor, July 14, to the author of the best memorial or unpublished essay on any branch of medicine deemed worthy of the prize.

NEW YORK

Committee to Aid in Survey.—A committee of the Medical Society of the State of New York has been appointed to cooperate with county medical societies concerning questionnaires in the survey of medical service now in progress under the sponsorship of the American Medical Association. Members of the committee, which was appointed by the president of the society, Dr. William A. Groat, Syracuse, are Drs. Oliver W. H. Mitchell, Syracuse, chairman; Herbert H. Bauckus, Buffalo; Frederic C. Conway, Albany; Charles Gordon Heyd, New York; Walter W. Mott, White Plains; Leo F. Schiff, Plattsburg, and Edward G. Whipple, Rochester.

New York City

Commission to Study Crippled Children.—A study of the care of physically handicapped children was launched recently with the appointment by Mayor La Guardia of a special commission with Dr. Philip D. Wilson, surgeon in chief of the Hospital for Ruptured and Crippled, as chairman. Dr. Vernon W. Lippard, associate attending pediatrician to the New York Hospital and instructor in pediatrics at Cornell University Medical College, has been selected to direct the survey, which will continue until July 1, 1939, and has obtained leave of absence from his other duties for that period. The first step will be the establishment of a registration bureau in the headquarters in the Lower West Side Health Center, 303 Ninth Avenue, Manhattan. The survey will analyze the type of care a child receives when once referred to a hospital or organization; it will also determine the extent of duplication of services and whether continued service is given to the handicapped child until he reaches maturity. The material thus gathered will be used in developing a program for proper physical, mental, educational and vocational care of these children, and the commission will have the right to recommend changes or revisions in the present set-up which may be considered necessary. Members of the commission are, in addition to Dr. Wilson, Drs. Alan De Forest Smith, Bradley L. Coley, Leo Mayer, Foster Kennedy, Herbert B. Wilcox, Howard R. Craig; Thomas S. McLane, treasurer, Association for the Aid of Crippled Children; Stanley P. Davies, director, Charity Organization Society; Lionello Perera, member, board of child welfare; Miss Katherine Faville, director, Henry Street Nursing Service, and Mrs. Adrian Van Sinderen, president, Brooklyn Visiting Nurse Association. Ex officio members are Dr. John L. Rice, city health commissioner; Dr. Sigismund S. Goldwater, hospital commissioner; Dr. Edward S. Godfrey Jr., Albany, state health commissioner; Harold G. Campbell, Ph.D., superintendent of schools, and William Hodson, welfare commissioner.

NORTH CAROLINA

Seminar on Tuberculosis.—The Buncombe County Medical Society held its second annual seminar on tuberculosis in Asheville July 11-16. Sessions were held partly in the Asheville Medical Library and partly in offices of several physicians, who gave special demonstrations and conferences. Among the speakers, all of Asheville, were Drs. Alfred Blumberg, "Pathology of Tuberculosis"; Thomas R. Huffines, "Tuberculosis of the Genito-Urinary Tract"; Paul H. Ringer, "Differential Diagnosis of Pulmonary Tuberculosis"; William P. Herbert, "Principles of Collapse Therapy," and Robert R. Ivey, "Emergency Surgery on the Tuberculous."

OHIO

Gift for Research at Ohio State.—Ohio State University College of Medicine, Columbus, has received a gift of $200,000 from the estate of Miss Marietta Comly, formerly of Columbus and Washington, D. C. Miss Comly's gift is a memorial to her father, the late Dr. J. W. Comly, and to her brother-in-law and sister, Dr. and Mrs. Nathaniel R. Coleman, Columbus. Dr. Coleman at his death bequeathed his medical library to the university and Miss Comly contributed $3,000 for additions to the library. Later she set up a trust fund of $20,000 for an alcove to house the Coleman collection. In 1929 she gave $1,000 for a student loan fund and in her will gave $5,000 more for that purpose. According to Dr. Charles A. Doan, chairman of the department of medicine and director of medical research, the income from the gift will be used to expand research programs already in progress at the college of medicine.

SOUTH CAROLINA

Secretary Hines Honored.—At the recent annual meeting of the South Carolina Medical Association at Myrtle Beach, the association presented to Dr. Edgar A. Hines, Seneca, a silver tray, pitcher and goblets in recognition of his long service as secretary and editor of the journal of the association. The presentation was made at the president's ball by Drs. Leonidas M. Stokes, Walterboro, president, and James R. DesPortes, Fort Mill, president-elect. Dr. Hines, who graduated from the Medical College of South Carolina in 1891, has been secretary since 1909 and editor of the journal since 1912. Among many activities Dr. Hines has been vice chairman of the state board of health for many years and was one of the founders of the board's bureau of child hygiene. In 1929 he was president of the South Carolina Pediatric Society. For many years he has been a member of the House of Delegates of the American Medical Association.

TEXAS

District Meeting.—The eleventh district of the Texas State Medical Association held a meeting in Athens recently with the following speakers, among others: Drs. George R. Herrmann, Galveston, "Modern Conceptions in the Diagnosis and Treatment of Hypertensive Arteriolar Disease"; Christopher B. Carter, Dallas, "Resection of the Recurrent Laryngeal Nerve in Tuberculosis of the Larynx"; Don Price, Athens, "Acute Suppurative Otitis Media," and Howard D. Cogswell, Tyler, "Treatment of Burns."

GENERAL

Broadcast on Accidents from Fireworks.—The National Society for the Prevention of Blindness prepared an electrical transcription of a ten minute program depicting dangers to eyesight from fireworks for presentation on and near the Fourth of July. The record includes an interview with Lewis H. Carris, managing director of the society, by Myron Weiss, associate editor of *Time*, and a brief dramatic sketch of a typical fireworks accident in which a boy is injured. The society offered the transcription free of charge to radio stations that desired to use it.

Society of Allergists.—The Ohio Valley Society of Allergists was recently organized with members from Indiana, Kentucky and southern Ohio. Dr. Albert R. Zoss, Cincinnati, was elected president and Dr. John Harold King, Cincinnati, secretary, at an organization meeting in Cincinnati last February. The spring scientific meeting was held in Cincinnati May 21-22 and was devoted to a discussion of fungi. Dr. Samuel M. Feinberg, Chicago, gave an address on "The Role of Air-Borne Fungi in Allergy." Other guests included Drs. Frederick W. Wittich, Minneapolis; John M. Sheldon, Ann Arbor, and Karl D. Figley, Toledo.

Society News.—The medical section of the American Life Convention held its twenty-eighth annual meeting at Asheville, N. C., June 16-18. Dr. Albert E. Johann, Des Moines, Iowa, was elected chairman, Dr. Maurice B. Bender, New York, vice chairman, and Dr. Benjamin F. Byrd, Nashville, Tenn., secretary.——Dr. Henry Chesley Bush, Livermore, Calif., was elected president of the National Tuberculosis Association at its annual meeting in Los Angeles June 21. Drs. Frederick T. Lord, Boston, and Paul P. McCain, Sanatorium, N. C., were elected vice presidents; President Roosevelt and Dr. Henry D. Chadwick, Boston, were elected honorary vice presidents. Dr. Charles J. Hatfield, Philadelphia, was reelected secretary.

Plan to Organize Society for Blood Transfusion.—Invitations are being issued to transfusionists and hematologists in the United States to join a national committee now being organized, the members of which will be members of an International Society for Blood Transfusion and Hematology now under consideration. At the closing session of the second International Congress on Blood Transfusion in Paris Sept. 29-Oct. 2, 1937, it was decided to establish the new society. It was agreed that each country form a national committee, the members of which are to form the international society. The purpose of the latter is to contribute to the advancement of scientific and practical knowledge concerning blood transfusion and blood studies by bringing together from the different countries those interested in these subjects. There is to be an international congress every three years, the next one to be held in 1940 in a city not yet selected. Dr. Lester J. Unger, 135 East Seventy-Fourth Street, New York, is secretary pro tem of the organization committee.

Assembly of Women's Field Army.—The first national assembly of the Women's Field Army of the American Society for the Control of Cancer was held in Kansas City in May in

conjunction with the national convention of the General Federation of Women's Clubs. Forty-three states were represented. The assembly opened with a dinner for state commanders at which the speakers included Mrs. Marjorie B. Illig, national commander; Clarence C. Little, Sc.D., managing director of the American Society for the Control of Cancer; Miss Alma Porter, executive secretary of the field army; Mrs. Grace Morrison Reynolds, Paducah, Ky., honorary national commander, and Arthur H. Estabrook, Ph.D., director of literature and exhibits for the society. There were also round table discussions and an open forum. A "hall of health" was presented during the week of May 10-18 under the supervision of Dr. Estabrook and Mrs. Illig, who is chairman of the health division of the federation of women's clubs. An extensive cancer control exhibit was included in the display and many state divisions of the field army had exhibits of their work.

Report of Golf Tournament in San Francisco.—One hundred seventy-nine medical golfers from all parts of the United States played the beautiful San Francisco Golf and Country Club course in San Francisco on the occasion of the twenty-fourth annual tournament of the American Medical Golfing Association, Monday, June 13. Ideal weather was scored and most of the entrants played thirty-six holes. The fifty-two trophies and prizes were awarded after the golfers' dinner, at which Dr. Walt P. Conaway, Atlantic City, N. J., president of the A. M. G. A., presided. Dr. James W. Morgan, chairman of the local golf committee, presented the prizes.

The championship was won by Dr. James J. Marek, Cleveland, who turned in a 76-80—156 for the thirty-six holes. He received the famous Will Walter Trophy, named in honor of the dean and organizer of the A. M. G. A., now of Charlottesville, Va.

The Handicap Championship was won by Dr. Rutherford T. Johnstone, Los Angeles, who bagged the Detroit Trophy, presented by the Detroit hosts in 1916.

The Eighteen Hole Championship went to Dr. Henry W. Milo, Mountain View, Calif., who took home the Golden State Trophy, presented by the San Francisco hosts in 1923. The Eighteen Hole Handicap Championship was awarded to Dr. Robert M. Harris, Miami, Fla., who won the Ben Thomas Trophy.

The Maturity Event, limited to Fellows over 60 for the best net score on the first eighteen holes, was won by Dr. William J. McGowan, Paducah, Texas, who won the Minneapolis Trophy. Other winners in this event were Drs. George H. Morris, Santa Maria, Calif.; Harry V. Hubbard, Plainfield, N. J., and Ream S. Leachman, Vallejo, Calif.

Dr. James Eaves, Oakland, Calif., first champion of the A. M. G. A. (at San Francisco in 1915) and president of the A. M. G. A. in 1924, won the Old Guard Championship awarded to past presidents, and received the Wendell Phillips Trophy. Another prize winner in this event was Dr. Walter F. Schaller, San Francisco, who was A. M. G. A. president in 1930.

The Championship Flight, low gross, was won by Dr. Duke R. Gaskins, Phoenix, Ariz., who secured the St. Louis Trophy. Other winners were Drs. Le Roy Brooks, San Francisco, and Roderic P. O'Connor, Oakland. The first net prize in this flight went to Dr. Lawrence A. Schueler, Los Angeles, who won the President's Trophy, a sterling silver pitcher presented by Dr. Walt P. Conaway. Dr. Erastus S. Edgerton, Wichita, Kan., was another winner in this event.

The First Flight gross winners were Drs. Robert C. Jamieson, Detroit; Henry D. Neufeld, Concord, Calif.; Quinter O. Gilbert, Oakland, and Walter B. Hardy, Birmingham, Ala. First prize among the nets was won by Dr. Edmund W. Butler, San Francisco; other prize winners were Drs. Harry E. Mock, Chicago; Leland H. Taylor, Oakland; Roscoe A. Ford, Los Angeles, and Smith A. Quimby, Madera, Calif. The Second Flight gross winners were Drs. August M. Brewer, Oklahoma City; James P. Warren and Edward F. Stadtherr, San Francisco, and Waltman Walters, Rochester, Minn. Net prizes went to Drs. Franklin G. Ebaugh, Denver; Francis B. Zener, Portland, Ore.; Joseph E. Bittner Jr., Yakima, Wash.; George A. Gray, San Jose, Calif., and George S. Johnson, San Francisco. The Third Flight winners were Drs. John R. Moritz, Beatrice, Neb.; Leslie L. Nunn, Vancouver, Wash., and William H. Bailey, Oklahoma City. The Fourth Flight winners were Drs. William J. Ryan, Duluth, Minn., and Samuel M. O'Connor, San Francisco. Fifth Flight winners were Drs. Stanley Dougan, San Jose, and Lewis A. Alesen, Los Angeles.

Drs. Merle G. Howard, Eugene, Ore., and David H. Houston, Seattle, were prize winners for excellent eighteen hole scores in the First Flight. In the Second Flight, similar prowess resulted in prizes for Drs. Cletus S. Sullivan and Donald R. Threlfall, both of San Jose, Calif. Other winners in the eighteen hole event were Drs. James G. Matthews, Spokane, Wash., and W. Albert Cook, Tulsa, Okla.

The Blind Bogey was won by Dr. Daniel P. Foster, Detroit, on a toss with Dr. Joseph V. Van Cleve, Wichita. Dr. Foster was presented with the Atlantic City Trophy, a sterling silver platter presented by the hosts of 1937. In addition to Dr. Van Cleve, other prize winners were Dr. Arthur C. McCarty, Louisville, Ky., and Dr. Ralph W. McKelvy, Los Angeles.

Election of Officers

Dr. Erastus S. Edgerton, Wichita, Kan., was chosen by unanimous vote as president of the A. M. G. A. for the ensuing year. Dr. George Washington Hall, Chicago, was reelected first vice president, and Dr. James W. Morgan, San Francisco, second vice president. The retiring president, Dr. Conaway, was made a member of the board of directors. The next meeting will be held in St. Louis at the time of the 1939 A. M. A. Annual Session.

The officers of the A. M. G. A. express their thanks to the many friends of the association who helped make the San Francisco tournament such a notable success. They are especially grateful to the San Francisco committee, which arranged all details so efficiently, and to the scores of prize donors, whose generosity is acknowledged.

FOREIGN

Congress on Rheumatism in New York in 1940.—At the International Congress on Rheumatism held at the University of Oxford, England, March 28-31, it was decided to hold the next congress in New York in June 1940. Dr. Ralph Pemberton, Philadelphia, was elected president. Subjects to be discussed will be the role of infection in rheumatic diseases, nutrition in rheumatism and the social significance of orthopedic work in rheumatic diseases. It was also resolved to hold a symposium on therapy in rheumatism.

Congress on Renal Insufficiency.—The second Congress on Renal Insufficiency will be held at Evian, France, September 21-24, under the auspices of the Medical Society of Evian. The official language will be French. A program of reports has been prepared and discussions may be presented. For the latter the titles must reach the general secretariat before August 1. For information address the General Secretariat, Deuxième Congrès de l'Insuffisance Rénale, 138 Avenue des Champs Elysées, Paris, or from July 16 to August 15, Direction Cachat, Evian-les-Bains, Haute Savoie, France.

Course in Malariology in Rome.—The Institute of Malariology in Rome is offering a course in malariology July 18 to September 17. The subjects to be covered are hematology, protozoology, malaria parasites and microscopic diagnosis, pathology of malaria, clinical malaria, entomology, epidemiology, prophylaxis, a survey of a malarious area and the results of malarial treatment of mental diseases. Various excursions to observe methods of malaria control in other cities have been arranged. The lectures will be in French and are limited to graduate physicians.

Cholera Epidemics.—Newspapers report that 17,330 persons have died of cholera in the United Provinces in the north of India in an epidemic reported to be one of the worst in many years. The number of cases reported June 26 was 35,000. Bodies of victims are thrown into the rivers that supply drinking water and religious Hindus, many infected with cholera, continue to bathe in the Ganges. Inadequate communication and transport facilities also hinder relief work in remote villages. Mass inoculation of exposed persons and disinfection of dwellings was reported to be under way.——Cholera has reached epidemic proportions in Shanghai, the Associated Press reported June 25. It was said there were 350 cases in the International Settlement and 145 in the French concession. Several cases were reported from Soochow, and 200 persons were said to have died in Swatow. A report July 10 stated that 1,728 Chinese have been stricken and 234 have died. The dispatch also reported that new cases are appearing at the rate of seventy a day. Millions are being inoculated.

LATIN AMERICA

Conference on Rural Hygiene.—An intergovernmental conference on rural hygiene will be held in Mexico City November 10-20. Topics selected for discussion include organization of rural medicine and health services (curative medicine, preventive medicine, health insurance and medical assistance in rural areas); selected problems of rural pathology; medical and health survey of a rural region; nutrition in rural districts; conditions of rural life.

Foreign Letters

LONDON

(From Our Regular Correspondent)

June 18, 1938.

Effects on Pregnancy of Operations on the Cervix

At the North of England Obstetric and Gynecologic Society Dr. J. W. A. Hunter made a plea for the use of more conservative treatment of endocervicitis and cervical lacerations in women of the child-bearing age instead of the extensive plastic operations which were becoming more common. The reports of cases of cervical amputation and repair showed such sequelae as sterility, repeated abortion and premature or obstructed labor. His interest in the subject began with seeing a patient whose cervix had been amputated. Seven abortions followed, and a first and living child was at last obtained after the patient consented to remain in bed from the onset of pregnancy. In the last nine months Dr. Hunter had encountered nine cases of abortion occurring for the first time after amputation of the cervix. He described eighteen cases of labor following cervical operation. In ten the labor was uneventful; in three cesarean section was necessary, in three vaginal cesarean section and in two manual dilation of the cervix. Three maternal deaths followed delivery, all being due to rupture of the cervical stump extending up to the lower uterine segment.

To minimize the danger of cervical plastic operations Dr. Hunter devised a modification of the usual plastic technic for prolapse in young women. It was used in cases of relaxation of all the uterine supports. He made one circular incision about one-half inch above the external os and another from 1 to 1½ inches above this, enabling a complete circle of vaginal skin to be removed. He then performed the customary anterior colporrhaphy and completed by suturing the cervix to the vaginal skin, beginning behind and working round to the front on each side. Thus the Fothergill principle of sliding the uterus upward and backward was maintained but with conservation of the cervix. Sometimes after the operation the uterus tended to remain in the vaginal axis. This could be remedied by opening the anterior peritoneal pouch and stitching the uterus to the peritoneum at the level of the anterior colporrhaphy or by performing Gilliam's suspension operation.

The Registration of Undertakers

In the House of Lords, Lord Horder moved the second reading of the funeral directors bill, which proposed to set up a board to control the training and admission to a register of persons who carried on the business of funeral directors. He said that it was in the public interest that the services rendered should be protected by such a board. Between death and the disposal of the remains there was a period in which no one was responsible, and to remove this anomaly the bill was framed. In recent years there had been a considerable advance in the knowledge, ability and capacity of undertakers. The bill was not well received. On behalf of the labor party Lord Strabolgi said that it would create a monopoly of persons who performed the last rites for the dead. Already the cost was too high. The minister of health should set up some department to watch over the disposal of the dead. The sanitary safeguards, which were one of the objects of the bill, were his duty. Viscount Samuel said that the great proportion of funerals were conducted by persons who were not whole time funeral directors. The effect of the bill on the customs of the village community must be considered. For the government the Earl of Munster stated that he was advised that there is no cogent medical reason for supporting the bill and that it might inflict hardship on poor persons in outlying areas. It was said that the bill would insure that undertakers had proper qualifications and would stop practices which caused pain to relatives, such as touting for orders, but he was advised that, on the contrary, the duties were carried out tactfully and decently. The government knew of no reason to warrant the conversion of this trade into a closed corporation. Lord Horder said that the bill did not place restrictions on half time undertakers, but in view of what had been said he would not press for a second reading.

The Chemotherapy of Pneumococcic Infections

The flood of articles on sulfanilamide and allied compounds and the success claimed for these new drugs has had no parallel since the introduction of arsphenamine by Ehrlich. There is the difference, however, that arsphenamine and its modifications were recommended for only one disease, while the question now is What are the infections which the sulfanilamide group do not benefit? One of the manufacturers has endeavored to prevent disappointment by giving in his pamphlet pulmonary tuberculosis, syphilis, malaria and typhus as infections for which no benefit is to be expected.

Experimental studies with a new compound 2-(p-aminobenzenesulfonamido) pyridine, have excited interest. They were made by Dr. L. E. H. Whitby, assistant pathologist, Bland-Sutton Institute of Pathology, and were reported in the *Lancet*. Substances of the sulfanilamide group active against the pneumococcus have recently been described but had the disadvantage of being toxic. The new compound has the great advantage of being relatively nontoxic and yet of protecting the mouse against 1,000 lethal doses of pneumococcus type I and affording considerable protection against the same dose of other types of pneumococcus. It is as effective as sulfanilamide is against hemolytic streptococci. It produces degenerative changes in the capsules of pneumococci. The manufacturers have stated that they have received numerous requests for the new compound but have refused to supply it until sufficiently controlled clinical research enables them to say with confidence in what directions it may be used with advantage.

PARIS

(From Our Regular Correspondent)

June 18, 1938.

Social Insurance and Private Practice

The city of Paris is divided into twenty wards for administrative purposes, and there is a branch medical society for each of these wards. At a special meeting May 18 of the branch society in the grand opera district, devoted to a discussion of the relation of the social insurance organization to the practitioner, a representative of the former, Dr. Martin, reviewed the law in force since 1930 but modified many times since. He pointed out that the government had no intention of making every practitioner a state official and then pleaded for more cooperation on the part of the profession. Dr. Heim de Balsac defended the free practice of medicine; that is, practice without any social insurance laws. He showed how the doctor-patient relation was an individual one and necessitated complete freedom of action on the part of both patient and physician. He strongly criticized the manner in which the law was carried out by the social insurance authorities and said that their disbursing offices insisted on an incredible amount of paper work. Furthermore, the fees allowed physicians for the medical care of the insured were ridiculously inadequate. Only hospitals which had made a contract with the social insurance organization could receive the insured, and they were very poorly paid. Patients were being driven away from physicians' offices and noncontract hospitals because they were compelled to be cared for by contract hospitals and dispensaries. This tendency on the part of social insurance to give medical care for practically nothing to one half of the population impressed the medical profession as inadmissible and not based on any social or valid legal principles. The speaker demanded that the disbursing offices which reimbursed the insured for medical, surgical, obstetric or dental attention should put a stop to this nefarious policy and attempt to collaborate in a loyal way with the profession.

Gonorrhea in the Female

The seventh French gynecologic congress was held at Nice under the presidency of Prof. Emile Chauvin of Marseilles. Almost the entire meeting was devoted to papers on gonorrhea in the female. Its relation to sterility was discussed by Dr. Claude Béclère of Paris, who reported having found endotubal lesions in 75 per cent of cases of sterility. In from 36 to 72 per cent they were due to chronic gonorrheal infection, which is responsible in 58 per cent of cases of sterility due to tubal occlusion. Tubal occlusion in turn is the cause in 50 per cent of all cases of sterility.

Dr. Maurice Fabre of Paris and his co-workers stated that it was necessary to keep constantly in mind the most common localizations; viz., the urethra, the cervix, Skene's glands and the rectum. Although much had been expected of vaccine treatment, this had not proved to be of much help. The present tendency to treat complications such as salpingitis conservatively had much in its favor. Even if operation became unavoidable, every effort should be made to conserve the ability of the patient to become pregnant and to menstruate. Vulvovaginitis and urethritis in adults were greatly benefited by diathermy. No better treatment had been found for skenitis and endocervicitis of gonorrheal origin than electrocoagulation. Radiotherapy in weak doses gave marked relief in cases of acute salpingitis. Of all physical methods, pyretotherapy, especially when short wave apparatus was employed, had yielded the best results until the advent of chemotherapy. In the discussion, Dr. Koenig of Geneva endorsed conservatism in the treatment of salpingitis, having observed a decided diminution in the virulence of the infection following expectant treatment. He had also employed radiotherapy and believed that operative intervention had been avoided as the result of its use. Dr. Loeser of London was enthusiastic regarding the use of cultures of gonococci, basing his conclusions on over 10,000 intradermal injections. He reported a cure in from 80 to 85 per cent of cases, complications having been observed in only 0.06 per cent, as compared to 0.27 per cent after the generally adopted methods of treatment. The intradermal injection of cultures produces an active immunization. Drs. Halphen, Auclair and Dreyfus of Paris employ a short wave apparatus for pyretotherapy. They raise the temperature to 41 C. (105 F.) for a total of fifteen hours, no treatment being less than four hours in duration. Their results have been highly satisfactory. Dr. Claude Béclère read a paper on diathermy and electrocoagulation in the treatment of gonorrhea in the female. A preliminary course of diathermy of the entire genital tract should be given, to last one month; then exocervical and endocervical electrocoagulation by the mono-active bipolar method should be used. In the third series of treatments, diathermy must again be given over the entire genital tract. This method has yielded the best results during the past four years at his clinic.

Dr. J. E. Marcel insisted on a different conception of localization of gonococci in vulvovaginitis in children. The urethra, cervix and often the rectum are also involved. The treatment of gonorrheal vaginitis in children with estrogenic substance has met with much opposition so far in France because of the fear of a harmful influence on the later evolution of the ovary. The author reported sixty-four cases treated with sulfanilamide. In some the disappearance of the gonococci took place rapidly; in others no result was obtained or there were recurrences. There were thirty-nine cures in sixty-four children. Drs. Gate, Michael and Delbos of Lyons reported the use of estrogenic substance in ten cases of gonorrheal and eighteen cases of non-gonorrheal vulvovaginitis in children. The results were satisfactory, especially when the condition was of gonorrheal origin, cure being obtained in eight of the ten cases.

The next congress will be held in Lille in the spring of 1939 under the presidency of Professor de Snoo of Utrecht, Holland.

BERLIN

(From Our Regular Correspondent)

May 23, 1938.

Meeting of German Society of Pediatrics

The German Society of Pediatrics met this year partly with the internists and partly by itself. Prof. Franz Hamburger, Vienna ordinarius, was chairman. The principal report, on "Convulsions in Childhood," was read by Walter Birk of Tübingen. He ascribed the predisposition in early childhood to convulsive attacks to various factors: cerebral injuries during birth with persistent lesions, the immaturity of the brain, the retarded development of the cortical region, the physiologic preponderance of the basal ganglions (pallidum) at this time of life and the peculiar significance of this cerebral region for convulsive attacks. A final consideration is frequent encephalitic foci which have defied diagnosis. In children beyond the nursling stage, spasmophilia and epilepsy have the most important roles. Between these two types of disorder are the so-called intermediate convulsions; e. g., tantrums and fever convulsions. The congress then discussed early spasmophilia of the newborn and late spasmophilia; namely, all cases of nursling spasmophilia which persist for years. Transition from spasmophilia into epilepsy does not occur. The term "circumstantial convulsions" is applied to attacks based on constitutional asthenia, disturbance of the vasomotor system and other nervous disorders, which are manifested under certain circumstances; e. g., excessive bodily fatigue, unusual mental strain and protracted standing in one spot. Pyknolepsy belongs to the last-mentioned class of convulsive states; it appears in its most classic form among children, continues for years, is manifested daily in many cases and tends to disappear completely. There may be a transition from pyknolepsy into epilepsy.

Willibald Scholz, Munich brain pathologist, discussed the pathology of the problem. It has not been possible to link any specific type or location of birth injury with the production of a specific type of convulsive state. Anatomy, physiology and so on furnish no satisfactory explanation for general predisposition to convulsions, although particular data are abundant in the literature. Scholz took up numerous pathologic details. At any rate, he said, we know that the vasomotor disturbances coexistent with convulsions may produce severe injuries to the brain. No cerebral lesions are demonstrable in simple loss of consciousness, pyknoleptic attacks and twilight states of epilepsy.

Georg Schaltenbrand of Würzburg said in the general discussion that in many cases of manifest epilepsy in adults there had been no anamnesis of epilepsy in youth.

A further chief topic was antirachitic prophylaxis. It has become recognized that the high incidence and importance of rickets call for general preventive measures against the disease. Artificial ultraviolet irradiation is conceded to be effective; the administration of vitamin D in milk is considered conditionally effective. Both of these methods, however, are too elaborate and costly for general use. Accordingly the administration of pure vitamin D is recommended above all as speedily effective and generally practicable. It was suggested that a national center for the campaign against rickets be established, the aims of which would be to protect every German child against the disease and to institute early treatment of rickets already developed. In the discussion the need for a more efficient prophylaxis was conceded. Rott of the national health bureau declared that incipient rickets must above all be brought under treatment. Supplementary prophylactic measures also are necessary. The groups most imperiled by rickets are infants born in the spring or summer and all children over 1 year of age with a debilitated constitution. In addition to the other measures suggested a systematic check-up of all nurslings for signs of rickets ought to be instituted.

Society for Study of the Circulation

The German Society for Study of the Circulation met in annual convention in March at Bad Nauheim. The chief topic was collapse and related pathologic conditions. Frau Gollwitzer-Meier spoke on the experimental pathology of circulatory collapse. The many definitions of collapse, which never correspond with one another, compel us to place in the foreground not the definition itself but the precise observation of the manifestations. Today a majority of investigators regard the formerly differentiated conditions of shock and collapse as belonging to the same clinical picture. In the pathogenesis of collapse the central circulation or the peripheral circulation may be principally involved, and humoral and nervous factors may also be differentiated. Among humoral factors histamine seems to play a conspicuous part, along with thickening of the blood and functional failure of the adrenals. The principal symptom of collapse is the decrease of the volume of blood in circulation, which in turn produces a diminution of the venous backflow. In collapse following trauma the histamine value is heightened in the venous blood of the injured parts. In collapse following burns an increase in the blood histamine is likewise demonstrable, so in both these conditions the substance must be of particular significance. Histamine causes first an ephemeral increase in minute volume, after which, because of the peripheral effect on the vascular wall, there is a decrease in minute volume accompanied by a fall in the blood and the venous pressure. Histamine exerts a constrictive effect on the large blood vessels. In the liver it induces contraction of the hepatic vein, but this cannot be the essential factor in shock, since histamine shock can be produced even after removal of the liver. In addition, histamine tends to irritate the terminal apparatus of the vagus within the heart. Furthermore, in collapse a decrease in the oxygenation of the arteries is demonstrable. Certain conditions favor the onset of collapse; e. g., narcosis, probably as a result of the concomitant capillary dilatation. In collapse one observes a decrease in body temperature that corresponds to the decrease in minute volume, as the production of heat is closely related to the circulation. The p_H of the blood also declines in collapse, and it remains depressed even after the blood pressure has risen.

Siebeck of Berlin discussed the clinical significance of collapse, reviewing the symptoms and referring, among other things, to the special role of the adrenal glands in collapse, as illustrated by the characteristic states of collapse in Addison's disease. The hypophysis, too, plays an important part in collapse. The cause of a collapse may be of cardiac origin, as, for example, in cardiac infarction and in postoperative collapse in cases of exophthalmic goiter. In the diagnosis of collapse it is often difficult to distinguish between a cardiac and a peripheral origin. Among signs of collapse based on heart failure are cyanosis, congestion, gallop rhythm and dilatation of the heart. Signs suggestive of peripheral circulatory failure are plasma deficiency, thickening of the blood, diminution of sodium chloride in the urine and abnormal turgor of the skin. First therapeutic measures are placing of the patient in a recumbent position, application of heat to the body, bandaging of the lower extremities, administration of brandy, applications to the precordial area and, especially for nocturnal attacks, administration of camphor. The most important measure is the intravenous administration of fluid infusions of sugar and sodium chloride. Massive blood transfusions are indicated for increase in the circulatory volume. Inhalation of a mixture of carbon dioxide and oxygen stimulates respiration and leads to evacuation of the blood depots. In any case circulatory collapse calls for an intensive, active offensive in which the most diverse procedures are utilized.

Kirschner of Heidelberg discussed the surgical aspects of collapse. He differentiated several types of collapse: 1. Collapse may take the form of heart failure with congestion and cyanosis. 2. There is vascular collapse. 3. Nervous collapse is a form. 4. Collapse may be due to loss of blood. 5. Collapse takes place during operation, often induced by latent lesions; postoperative fatalities are usually due to collapse. Prophylaxis consists in timely support of the circulation and precautions against chilling, loss of blood and starvation before the operation. Undue exertions, e. g., walking to the operating room and too early getting up after operation, are to be avoided. 6. Patients are in particular danger of collapse who have sustained trauma of the thorax, abdomen, spinal cord or brain. If collapse threatens, the surgical intervention should be reduced to a necessary minimum or performed in two stages. Use of the electric knife is also recommended. Other important remedies are stimulation of peristalsis by means of the intestinal tube and by injections of solution of posterior pituitary, as well as by complete abolishment of pain. An important consideration is the type of narcosis employed; rectal narcosis or intravenous narcosis is often safer than other types. 7. Collapse is especially likely to occur in a patient under lumbar anesthesia; the more extensive the anesthesia the greater the danger. Collapse readily appears in the presence of gas phlegmon and of suppurative processes within the thoracic and abdominal cavities, because of the extensive areas of toxic absorption.

On the second day Eppinger of Vienna discussed "Modifications of Permeability of the Capillaries," on the basis of his investigations of histamine collapse. By means of a new technic of staining the author was able to demonstrate the proteinic nature of the fluid in the tissues during collapse. The capillary membranes become permeable for protein during histamine collapse. In severe gastroenteritis severe changes occur in the hepatic capillaries which lead to an outflow of protein from the blood into the perivascular interstitial clefts and to serious destruction of liver cells. Furthermore, this serous inflammation can lead to acute yellow atrophy and to cirrhosis of the liver. It therefore seems probable that through the production of severe vascular lesions the serous inflammation may represent the initial stage of cirrhosis of the liver. Vascular damage is also demonstrable in man in the vessels of the extremities. Permeability of the ions too is altered. In contrast to the normal condition, one finds during anaphylactic shock that a large amount of potassium is present in the body serum and a small amount of sodium is present in the cells. The emigration of potassium and the influx of sodium produce the picture of cloudy swelling. Similar processes take place in the musculature during fatigue. Thus, Eppinger concluded, there are gradual transitions from fatigue to inflammation to death.

BUDAPEST

(From Our Regular Correspondent)

May 19, 1938.

Fever Treatment of Neurologic Conditions

During the national medical week, Dr. Stephan Somogyi reported the experience of the Budapest neurologic and psychiatric clinics in the fever treatment of mental and nervous diseases of more than 1,000 patients. Hyperpyrexia was induced in 873 instances: with malaria in 550, with drugs in 135 and with injections of milk in 188. Malaria therapy proved the most efficacious. Somogyi holds that the hyperpyrexia itself is the most important factor. In the treatment of manic-depressive psychosis, schizophrenia and epilepsy there were no conclusive results. With tabetic dementia paralytica some improvement of symptoms was noticeable, chiefly relief from the lancinating pains and the crises; with the chronic forms of epidemic encephalitis and with disseminated sclerosis the results were poor. In contrast, fever therapy was effective in the treatment of chorea minor, dementia paralytica, acute trigeminal neuralgia, acute peripheral facial paralysis and sciatica.

Industrial Cutaneous Diseases

A Hungarian public health journal directs attention to a number of special industrial diseases of the skin encountered in Hungary. Anthrax is found in tanneries and brush factories.

Chrome ulceration resulting from the handling of sodium and potassium bichromate, used in dyeing, is well recognized; the earliest symptoms are boils, pimples or eczema; the final ulcers occur on the mucous membrane, e. g., of the nose, as well as on the skin of the hands. Cutaneous diseases in the form of eczema are common among workers with aniline dyes; they are often accompanied by blepharitis, conjunctivitis and onychia. Rules enjoining strict personal cleanliness resulted in improvement in a factory which was kept under careful supervision. Workers in arsenic, much used as a coloring agent in some industries and in wallpapers, often have an eruption, with ulceration when it is neglected; the hands, forearms, neck and nostrils are affected chiefly and the thighs, feet and scrotum occasionally. Laundry women's eczema is due to the strong alkalis, or bleaching solutions, used in laundry work; infection may result also from the handling of infected clothes. Flax spinners are subject to an eczema which is ascribed to oils in the flax. Chemical manufacturers and druggists are exposed to many irritating substances, of which quinine is mentioned as often being responsible for dermatitis. Lime juice makers and persons handling bitter oranges are subject to a form of dermatitis which may be complicated by headache, neuralgia, giddiness and cramps. The list of workers subject to special cutaneous diseases includes bronzers, electroplaters, matchbox makers, polishers, cabinet makers, glue makers, brush makers, leather dressers, tanners, furriers, plasterers, steel grinders, smelters, cement makers and tar workers.

AUSTRALIA

(From Our Regular Correspondent)

June 1, 1938.

National Health Insurance Difficulties

A deadlock has arisen between the medical profession in Australia and the federal government. Before the introduction of the national health and pensions insurance bill, the executive of the federal council of the British Medical Association agreed to certain of the government's proposals in the bill, including the acceptance of a capitation fee of 11 shillings per annum for all insured persons. It was made clear at the time, however, that the federal council could not bind its members by any agreement that had been reached and that, in any matter with such a wide scope as national insurance, members of the association throughout Australia ought to be consulted. The members have now made it clear that there is a great deal of opposition to some of the provisions of the bill, and certain amendments have been suggested to the government. The government, on the other hand, refuses to alter its original plans.

The main bone of contention concerns the amount of the capitation fee. It is considered by members of the medical profession that the 11 shilling fee is quite inadequate remuneration for a general practitioner service in this country and that 14 shillings per annum in metropolitan areas and an additional 25 per cent per annum in country districts are the minimum rates acceptable to the profession. Proposed mileage rates are also considered unsatisfactory. The present proposal allows a practitioner one trip a year to each insured patient at the rate of 1 shilling per mile (after 3 miles) whether the trip is made or not. The profession has suggested a minimum rate of 2s. 6d. per mile (one way only) for every trip made, sixpence of which should be payable by the patient. Under lodge contract practice in Australia, mileage is always payable by the patient as a deterrent against unnecessary calls. There is universal dissatisfaction with regard to the absence of night fees. It is thought that some fee, not necessarily large—2s. 6d. is suggested—should be charged for night calls, to act as a restriction on the amount of night work. Finally, a clear definition of general practitioner service is required.

The government has refused to make these amendments or even to consider temporary acceptance of the original proposals by the profession pending adjustment after several years' trial, on the ground that such alterations would interfere with the actuarial basis of the scheme. Nevertheless, two major amendments have been made affecting other sections of the community: the extension of benefits to dependents through a voluntary scheme, at an estimated cost to the government of £175,000 a year, and an increase in pension payments for women. The profession has also taken a firm stand in the matter. Plebiscites taken in several of the states show a large majority against the acceptance of the 11 shilling capitation fee, and many local branches of the British Medical Association have stated that their members are not prepared to work under the scheme as at present proposed. It has been calculated that if the scheme was in operation an average practitioner's net income would approximate £665 per annum. This reckoning has taken into consideration all sections of the community and probable sources of income. This income is not high in a profession so costly to enter and in which hours are so unlimited. Cooperation between the government and the medical profession is essential if national insurance is to be successful.

Sir Walter Kinnear Called to America

Sir Walter Kinnear, expert on British national insurance, who is now at Canberra, has been requested by the United States government to offer his advice concerning difficulties which have arisen in the administration of the United States social security act. He will probably leave for Washington, D. C., as soon as the commonwealth national health and pensions insurance legislation has been passed. Sir Walter was in charge of the British national insurance department when he came to Australia, two years ago, to report on a similar scheme for this country. He retired on his return to England, and his services were then obtained by the commonwealth to assist in the drafting of the legislation now before parliament. Sir Walter Kinnear has marked ability and extensive experience in the administration of national insurance; the chief Australian criticism of his outlook is that he has endeavored to fit rather too closely the details of the British system to Australia. It is claimed by persons who have studied conditions in both countries that the general standard of medical practice is higher in Australia than in Great Britain. There has never been any medical practice in Australia comparable to that of the cheap "club" doctors who used to exist in Britain, and anything would have been an improvement on such practice. There is a general feeling that national insurance may tend to lower the Australian standard of general practice if British conditions are too rigidly imposed.

Marriages

DANIEL HERTZ FUNKENSTEIN to Miss Hannah Bessie Harris, both of Macon, Ga., in Jacksonville, Fla., June 21.

OTTO S. DOWLEN JR., Miami Beach, Fla., to Miss Richardine Massey of Birmingham, Ala., June 21.

ARTHUR F. TOOLE, George School, Pa., to Miss Barbara Reagan in Brookline, Mass., June 18.

SAMUEL GWIN MOUNGER, Yazoo City, Miss., to Miss Catherine Davis in Oxford, June 18.

WALTER JEROME LEE to Miss Lenore McFall, both of Nashville, Tenn., at Winchester, June 25.

CLARK HOUSTON GILLESPY to Miss Orlean Lowry Drennen, both of Birmingham, Ala., in June.

VICTOR B. LAMPKA to Miss Emily Patricia Swierczynska, both of Buffalo, July 12.

JAMES ALANSON MOORE, Boston, to Miss Eleanor MacLeod of New York recently.

DORIS E. JOHNSON, Youngsville, Pa., to Mr. Raymond L. Fales, April 15.

JOHN B. VARNER to Miss Theodore Davis, both of Atlanta, Ga., in June.

Deaths

Henry T. Williams ✠ Rochester, N. Y.; University of Pennsylvania Department of Medicine, Philadelphia, 1881; fellow of the American College of Surgeons; at one time secretary of the Rochester Academy of Medicine; consulting surgeon to St. Mary's and Monroe County hospitals and Monroe County Penitentiary; honorary surgeon to the Rochester General Hospital; aged 80; died, April 26, of chronic myocarditis.

John Champlin Jr., Westerly, R. I.; Tufts College Medical School, Boston, 1922; member of the Rhode Island Medical Society; fellow of the American College of Surgeons; at one time chairman of the state public health commission; secretary and past president of the Washington County Medical Society; on the staffs of the Westerly Hospital and of the South County Hospital, Wakefield; aged 41; died, May 2.

Jennings Meade King ✠ Pittsburgh; Western Reserve University Medical Department, Cleveland, 1921; member of the American Academy of Orthopedic Surgeons; demonstrator in orthopedic surgery, University of Pittsburgh School of Medicine; aged 39; on the staffs of the Presbyterian Hospital, Children's Hospital and the Western Pennsylvania Hospital, where he died, April 8, of pneumonia.

Albert Jefferson Caldwell, Amarillo, Texas; Kentucky School of Medicine, Louisville, 1892; member of the State Medical Association of Texas; past president and secretary of the Potter County Medical Society; served during the World War; aged 70; on the staff of the Northwest Texas Hospital, where he died, May 7, of carcinoma of the pancreas.

Charles Jeffry Pick ✠ New York; Bellevue Hospital Medical College, New York, 1896; member of the American Society of Anesthetists; on the staffs of the Mount Sinai, Sydenham, Jewish Memorial and the Beth David hospitals and the Hospital for Joint Diseases; aged 63; died, April 22, of carcinoma of the gallbladder with metastases.

Wesley Cornelius Redd, Youngstown, Ohio; University of Pennsylvania School of Medicine, Philadelphia, 1917; member of the Ohio State Medical Association; served during the World War; aged 49; died, April 16, in St. Elizabeth's Hospital of chronic myocarditis, aortitis, chronic nephritis, hypertension and pneumonia.

Bert E. Loehr, San Jose, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1909; member of the California Medical Association; past president of the Santa Clara County Medical Society; aged 56; on the staffs of the Santa Clara County Hospital and the San Jose Hospital, where he died, April 12.

Orville Joseph Sloan ✠ Glendale, Calif.; University of Nashville (Tenn.) Medical Department, 1907; fellow of the American College of Surgeons; on the staffs of the Physicians and Surgeons Hospital, Glendale, and the Los Angeles County General Hospital; aged 52; died, April 30, of myocarditis and arteriosclerosis.

Benjamin Richard Johnston, Cedar Rapids, Iowa; Hering Medical College, Chicago, 1893; at one time professor of theory and practice of medicine and clinical medicine at the State University of Iowa College of Homeopathic Medicine; served during the World War; aged 71; died, April 13, of cerebral thrombosis.

Adrian Richard Alfred ✠ Medical Director, Captain, U. S. Navy, retired, Long Beach, Calif.; University of Michigan Department of Medicine, Ann Arbor, 1889; veteran of the Spanish-American and World wars; entered the navy in 1890 and retired in 1928; aged 73; died, April 17, of coronary occlusion.

Edward Schifferle ✠ Creston, Iowa; Rush Medical College, Chicago, 1884; an Affiliate Fellow of the American Medical Association; for many years connected with the relief medical employment and pension department of the C. B. & Q. Railroad; aged 80; died, April 16, of cholecystitis with cholelithiasis.

John Ritter ✠ Miami, Fla.; Rush Medical College, Chicago, 1880; assistant professor emeritus of medicine at his alma mater; member of the Illinois State Medical Society; author of "Handbook of Tuberculosis for Medical Students and Practitioners of Medicine"; aged 84; died, May 23, in Springfield, Ill.

Charles Byron Drake, West Lebanon, N. H.; Dartmouth Medical School, Hanover, N. H., 1883; member of the New Hampshire Medical Society; at various times a member of the state legislature, board of education and state board of health; school physician; aged 89; died, April 2, of pneumonia.

Jonathan Mellen Mansfield, Clinton, Iowa; State University of Iowa College of Medicine, Iowa City, 1917; member of the Iowa State Medical Society; served during the World War; aged 45; on the staff of the Jane Lamb Hospital, where he died, April 28, of uremia and nephritis.

Milo Orion Brush ✠ Shenandoah, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1908; served during the World War; member of the board of education; on the staff of the Hand Memorial Hospital; aged 53; died, April 23, of lobar pneumonia.

Harry Cryndlon Buster, Baldwin, Mich.; Northwestern University Medical School, Chicago, 1910; member of the Michigan State Medical Society; served during the World War; aged 57; died, May 15, in Chicago, of essential hypertension and cerebral hemorrhage.

Ida Catura Coler, Long Beach, Calif.; Woman's Medical College of Baltimore, 1888; University of Michigan Homeopathic Medical School, Ann Arbor, 1899; aged 81; died, April 13, in the Seaside Hospital, of pulmonary edema, cerebral arteriosclerosis and thrombosis.

Oliver Kidwell Speer, Tamaqua, Pa.; Medico-Chirurgical College of Philadelphia, 1894; member of the Medical Society of the State of Pennsylvania; served during the World War; aged 67; died, April 23, in the Jefferson Hospital, Philadelphia, of carcinoma of the esophagus.

Elmer Llewellyn Dickey ✠ Oil City, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1894; fellow of the American College of Surgeons; served during the World War; on the staff of the Oil City General Hospital; aged 72; died, April 4, of heart disease.

Daniel Armstrong Atkinson ✠ West View, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1901; county medical director; aged 62; on the staff of the Suburban General Hospital, Bellevue, where he died, April 3, of agranulocytosis.

Edward Augustus Sheafe ✠ Ottumwa, Iowa; State University of Iowa College of Medicine, Iowa City, 1894; past president of the Wapello County Medical Society; formerly city physician; aged 76; died, April 18, of uremia.

Melvin Pirl Badger ✠ Manchester, N. H.; University of Vermont College of Medicine, Burlington, 1909; served during the World War; on the staff of the Notre Dame Hospital; aged 51; died, April 23, of pulmonary thrombosis.

Ralph James Critchfield, Fargo, N. D.; University of Minnesota Medical School, Minneapolis, 1922; served during the World War; aged 48; died, May 3, in the Veterans Administration Facility, St. Cloud, Minn., of pneumonia.

Eugene Martin Holden, Otisfield, Maine; Harvard University Medical School, Boston, 1890; member of the Massachusetts Medical Society; aged 77; died, April 9, in Cambridge, Mass., of lobar pneumonia and arteriosclerosis.

James Arnot Walker, Youngstown, Ohio; Jefferson Medical College of Philadelphia, 1918; member of the Ohio State Medical Association; aged 49; was found dead, April 5, of acute dilatation of the heart and endocarditis.

Christopher C. Gardner, Braddock, Pa.; University of Pittsburgh School of Medicine, 1909; served during the World War; on the staff of the Braddock General Hospital; aged 51; died, April 29, of coronary thrombosis.

Maurice Joseph Spiegel ✠ Los Angeles; University of Illinois College of Medicine, Chicago, 1932; aged 39; died, April 21, in the Cedars of Lebanon Hospital, of injuries received when struck by an automobile.

Isaac Barton, Philadelphia; Jefferson Medical College of Philadelphia, 1877; member of the Medical Society of the State of Pennsylvania; aged 81; died, April 2, of angina pectoris.

Anthony Juliano, Philadelphia; Maryland Medical College, Baltimore, 1912; aged 49; died, April 7, in the St. Luke's and Children's Hospital of gangrene of the right foot and leg.

Louis von Cotzhausen, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1885; aged 84; died, April 24, in the Hahnemann Hospital, of pneumonia.

Margaret Caldwell, Waukesha, Wis.; Woman's Hospital Medical College, Chicago, 1876; member of the State Medical Society of Wisconsin; aged 92; died, May 4, of senility.

Thomas B. Turner, Swedesboro, N. J.; University of Pennsylvania Department of Medicine, Philadelphia, 1875; aged 90; died, April 6, of pneumonia and prostatitis.

Eugene Underhill, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1893; aged 77; died, April 4, of uremia.

Correspondence

CONTROL OF MENINGITIS

To the Editor:—The article on the "Control of Meningococcic Meningitis Epidemics" by Dwight M. Kuhns and others in the February 12 issue of THE JOURNAL will provide clues for future study in preventive medicine. However, the article did not lead to any definite conclusions as to the value of a program of active immunization in a closed population group. According to the article, forty-eight different camps were involved with an average population of 152 per camp. In table 3, twenty different outbreaks were listed: in nine, or 45 per cent of the series there occurred only a single case. Does such an incidence constitute an epidemic, or could not one anticipate such a rate to occur by chance in any other comparable group under similar circumstances? Estimates have been made that from 2 to 5 per cent of the population in camp enrollees are normally carriers and that the attack rate in any population is approximately 1 per cent. In table 3 attack rates varied from a low of 0.21 per cent to a maximum of approximately 5 per cent. Closer scrutiny of the figures showed that in only five instances had the attack rates exceeded approximately 1.5 per cent. Consequently in 75 per cent of the outbreaks cited the attack rates were within approximately normal limits. In another paragraph the authors cited the occurrence of three cases in a group of 1,612 plus-minus and negative reactors. This is an attack rate of only 0.18 per cent, well within the normal limits and truly not a significant comparison when contrasted with the failure of cases to occur in the actively immunized group.

If complete active immunization required a total of sixteen days (four doses at four day intervals), a period within the average incubation period of the disease, and if during this period other factors for the control were presumably instituted, was it correct to assume that active immunization by the toxin was responsible for the subsidence of the outbreak? Could not isolation management of the clinical cases and of the suspected carriers, the correction of overcrowding, wider floor space between beds and improvement of the general hygienic and sanitary conditions all have contributed to the control? What would have been the attack rate if the same program had been followed without the active immunization?

Dr. Kuhns and his co-workers stated that twenty-six cases occurred in a period of two years prior to instituting their active immunization program, and none since. It would be of interest to ascertain whether all of the enrollees in the various camps were permanent members during that entire period or if there were new additions to the camp population from time to time to replace those discharged. Is it not possible to conceive that many of the new members were not necessarily susceptible to the disease? Some of the new enrollees might have developed various degrees of immunity resulting from subclinical infective doses in the general population prior to their enlistment, and consequently the population groups were not truly comparable. Furthermore, what changes had occurred in the various camp managements as to sanitation, hygiene, overcrowding, the building up of the resistance of the population and so on during the past two years, besides the immunization program instituted? Did not all these factors play a role, and the immunization program serve only as an adjunct? Cognizance must be taken that outbreaks of epidemic meningitis occur in cycles. It would be of value to ascertain for comparative purposes the general attack rate of the disease throughout the United States and in the various states in which the camps were located.

In two outbreaks cited by the authors (Boys' Training School in Oklahoma and the Kansas City Boys' Orphanage) they state ". . . this illustrates the use of the toxin in both an explosive and chronic type of outbreak." What is meant by a chronic type of an outbreak; did it denote a normal expectancy of occasional cases and, if so, what was considered the average per year? Has the use of the toxin indicated its true value? The authors concluded with the statement ". . . therefore it is important that every control measure available be used as early as possible after the appearance of the first case." Under such circumstances, can any active immunization program be given complete credit for the control of an outbreak of epidemic meningitis?

In table 2 the question was raised as to the value of immunization. If in a group of 3,773 cases immunized only 1,163, or approximately 33 per cent, resulted in negative reactions, was such a procedure of value? For the purpose of prophylaxis during an outbreak, all plus-minus reactors would have to be included with the group that gave a one plus or greater reaction. Consequently instead of 78.9 per cent change from positive to negative reactors as cited there were approximately 67 per cent positive reactors who must be considered susceptible to the disease, as determined by the cutaneous test. It is important to ascertain how soon protection begins after immunization has been completed and what the duration of such protection is.

The total camp enrolment was arbitrarily segregated into two classifications, namely, (1) those enrollees who showed a one plus or greater reaction (3,926) and (2) those who gave a negative result (3,413) and who apparently were considered the control group. The value of the effectiveness of the immunization program would have been enhanced if a control series had been established among the group of positive reactors. As a result, if one half of the positive reactors, approximately 1,963, could have been immunized and a similar number of the positive group nonimmunized, the latter would have served as actual controls. Consequently, if these two groups of former positive reactors had been retested in two months (one group immunized and the other not) it would have been possible to determine the difference in the percentage of those giving a reaction of one plus or greater, a plus-minus or a negative result. Under these circumstances, if the percentage of negative reactors had been significantly greater in the immunized group than in the immunized group of the previously positive reactors, the value of prophylactic immunization would probably have been proved.

Comparison of the percentages of the case incidence in the immunized and the nonimmunized groups were indeed instructive and enlightening. In the group of 3,773 patients immunized no cases occurred, a result of 100 per cent. In the nonimmunized group of 3,566 cases (the difference between 7,339 patients tested and 3,773, the number of patients immunized), there occurred twenty-six cases, a result of 99.5 per cent. Surely such a small difference can be of no significance in the evaluation of the final results.

I wish to cite Riding and Corkill (Prophylactic Vaccination in Epidemic Meningococcal Meningitis, *J. Hyg.* **32**:2 [April] 1932) and their work on immunization in epidemic meningitis. In an outbreak studied in the North Sudan district they had the opportunity to observe the effects of such a program in a more or less closed population group. In the cities of Deims and Khartoum of a total of 9,713 people who were inoculated with vaccine A (type 2, the predominating strain) there occurred seven cases and five deaths, while in a group of 9,720 inoculated with vaccine B (typhoid and paratyphoid A and B) there were ten cases and seven deaths. The authors say "In Khartoum City no cases or deaths from meningococcal meningitis occurred among the subjects inoculated with the meningococcal vaccine (vaccine A), while there were 1.06 cases and 0.71 deaths per 1,000 from the disease among those inoculated with the T. A. B. vaccine (vaccine B), a result apparently favorable to the use of vaccine A as a prophylactic.

When the figures are subjected to statistical analysis, however, it is found that the standard deviation is 1.731 and the difference between the number of cases in the two groups is less than twice the standard deviation, giving odds against the result being due to errors of sampling of less than 22 to 1. The absence of significance in this finding is supported by the result in Deims, where there were 0.98 cases and 0.70 deaths per 1,000 in the vaccine A group, and 1.01 cases and 0.72 deaths per 1,000 in the vaccine B group; that is, no appreciable difference between the two groups." Consequently, prophylactic vaccination as applied under strictly experimental conditions in an epidemic proved ineffective as a means of controlling the disease.

How much reliability can be placed on the cutaneous test? Is it of a specific and of a diagnostic significance? If during the procedure the strength of the toxin is increased from 1:200 to 1:20, does one obtain an accurate picture? What is the basis for the amount and the strength of the toxin used intradermally? When the former dilution was used, the proportion of positive reactors was 53 per cent but when the stronger dilution (1:20) was substituted the proportion of positive reactors increased to 99 per cent. Does the reaction to the toxin constitute the degree of susceptibility? Is it not possible that the increased percentage of positive reactors thus observed was only an indication of the reaction to the strength of the toxin used? Can the tolerance that a normal individual demonstrates to the strength of the injected dose serve as a basis of susceptibility of the host to the disease? A positive reaction does not necessarily indicate that such a reactor will become a clinical case but is merely susceptible. Due consideration must be given to the virulence and invasive power of the organism and its infective dosage as well as to the resistance and susceptibility of the host.

I believe that, first, active immunization is of questionable value during impending outbreaks of epidemic meningitis as shown by statistical comparison. Equally good results can be obtained by proper isolation management and by improvement of the sanitary and hygienic conditions of the area and population in question.

Second, the cutaneous test as cited by the authors changed positive to negative reactors in only 33 per cent of cases, not a significant rate during times of an outbreak.

Third, one significant factor must not be overlooked; namely, the carrier problem. If the chronic intermittent carrier can be detected and isolated, an outbreak may cease as abruptly as it began.

Finally, one must determine what constitutes an outbreak of epidemic meningitis. Therefore a great deal more work remains to be done in the control of epidemic meningitis, before any definite conclusions are warranted concerning the use and value of active immunization with meningococcus soluble toxin.

GEORGE PARRISH, M.D., Health Officer,
Los Angeles City Health Department.
By HYMAN I. VENER, M.D., C.P.H.,
Assistant Epidemiologist.

This letter was referred to Dr. Kuhns, who replies:

To the Editor:—Theoretically the suggestions of Drs. Parrish and Vener for the control of epidemic meningitis appear quite plain, but practically we found that, after applying the sanitary control measures mentioned by Dr. Vener and outlined by us in our preliminary report July 4, 1936, in THE JOURNAL, additional cases continued to occur. Apparently Drs. Vener and Parrish did not possibly read or see our preliminary report. In that paper practically all the questions they have suggested have been answered at some length. In the preliminary report we showed that isolating all the carriers would be difficult if not impossible. We found almost as many carriers in a control camp as we did in the epidemic camp.

Recently Rake's experience in culturing (*J. Exper. Med.* **61**:545 [April] 1935) from the Rockefeller Institute was interesting. He found ninety-seven positive carriers in 215 CCC enrollees. (The number of carriers found usually is in direct proportion to the intensitiveness of the culturing.) After finding all these positive carriers, their final solution to the control of the epidemic was to send all the enrollees to their respective homes.

Lieutenant Colonel Simmonds states that during the World War their experience demonstrated the futility of culturing and isolating all the carriers.

Dr. Rosenau summarizes the present status of sanitary control measures and culturing as means of control of meningitis much in accordance with the views of administrators I have known both in and out of the army. He says:

> In military practice, the isolation of meningitis carriers is not only extravagant and against military efficiency, but also impractical and noneffective.
>
> We must frankly admit that when cerebrospinal meningitis has once become epidemic it cannot be stamped out by any known means of practical application.
>
> This does not mean that we should assume a supine attitude, for, even though the disease cannot be satisfactorily controlled, a certain number of secondary cases may be prevented. Vaccines have been tried, but their usefulness has not been established. *The procedure is logical and deserves extended observation.* Agglutinins develop in the blood of those vaccinated.

The following is some of the evidence why we believe and still believe that meningococcus soluble toxin will aid in raising the immunity of the individual:

1. The individual himself by recovering from the disease is able to produce sufficient immunity to recover from a disease produced by a specific organism.

2. Meningococcus antitoxin serum has been found to be effective by Hoyne of Chicago in reducing a mortality from 50 per cent to 10 per cent in meningococcic meningitis. If an active immunity can be produced in horses and that serum cause a recovery in human beings it would indicate that an active immunity might be brought about in man.

3. Ferry in 1931 found that animals could be protected both by passive and by active immunity against meningococcic infection.

4. Dr. John A. Kolmer has recently reported (*Am. J. Clin. Path.* **8**:1 [Jan.] 1938) his results in protection of experimental meningococcic meningitis by the use of whole broth culture (vaccine and soluble toxin) which we mentioned in our preliminary report.

Against lethal doses of meningococcus he protected 23 per cent of guinea pigs and 46.4 per cent of rabbits. Against symptoms he protected 77.0 per cent of monkeys. A study of his report presents no evidence why immunity in man cannot also be produced.

5. In our preliminary report (table 7) we showed that a patient with a positive cutaneous test at the onset of the disease was negative on recovery. Since this first report we have confirmed this finding in five additional cases. This is one of our most convincing experiments in that the toxin we are using was neutralized or antibodies were produced against it when an individual recovered from the disease.

6. Table 8 in the same report showed negative reactions to the cutaneous test with meningococcus soluble toxin in six convalescent cases.

7. Cutaneous tests by Ferry, ourselves and others have shown a trend from positive to negative following active immunization.

8. Finally, the most suggestive evidence that we have that the meningococcus soluble toxin may confer protection to human beings is that in twenty different places where cases occurred exposing groups that would ordinarily be considered susceptible the soluble toxin was given with only one additional case occurring. In other words, it would be rather difficult to conceive how one could select twenty outbreaks for immunization and give the toxin at the time when no additional cases were going to occur.

Dr. Ferry of Parke, Davis & Co. wrote recently and stated that I had said "to establish the best possible immunity against epidemic meningitis a greater antibody producing substance was needed." Dr. Ferry comments further: "I notice that of all individuals injected you had but one case following the treatment. That looks like a pretty good record. How would one go about to improve it?" I understated the case purposely to stimulate others to study the soluble toxin further.

Drs. Vener and Parrish indicated in their analysis that since a meningococcus vaccine had been proved to be noneffective the same would apply to the soluble toxin. This suggests that they apparently missed the reason for our using the soluble toxin. To compare the soluble toxin with the vaccine would be like comparing diphtheria toxoid with a diphtheria vaccine. The bacteria in our first paper were shown to have very little antigenic value. It was due to the excellent results obtained by Dr. Ferry with his meningococcus antitoxin that we were led to give the soluble toxin a trial.

The occurrence of meningitis during the World War varied from 0.3 to 6.6 per thousand in thirty-nine concentration camps and ranked sixth as the cause of death.

Dr. P. M. Stimson of Cornell University, in his manual entitled "Common Contagious Diseases," 1936, page 290, states that an attack rate in a general population of 1 per thousand is rare. Our rates varied from 21 to 50 per thousand in unimmunized enrollees and only one case developed in 7,511 immunized enrollees reported. In approximately 3,000 enrollees immunized since then no cases have occurred. If we can continue to keep our attack rate at this level in concentrated and exposed groups we shall be very fortunate indeed. However, no conclusions can be drawn from our attack rate, owing to the fact that soluble toxin was given as early as possible in each outbreak.

As the result of the ease of making this soluble toxin and the absence of reactions in the individuals receiving it and with the evidence accumulated that immunity can be produced by the toxin in living tissue, we feel as many others that every effort should be extended to encourage the use of the soluble toxin and the development of a more patent immunizing product.

In summary I give the following vital points as to why the immunity of the individual should be raised in controlling meningitis:

1. Sanitary measures have been tried but in themselves are insufficient to prevent further occurrence of cases.

2. Control of carriers by culturing at the present time is considered ineffective.

3. Epidemic meningitis still remains a definite preventive medicine problem which may cause the physician in charge not only considerable administrative embarrassment but actual loss of life beyond his control.

4. The soluble toxin is a new form of antigen which practically, both experimentally and clinically, has yielded excellent results, that is, no further cases occurred in individuals exposed after immunization in closed populations during an outbreak.

At present I know of no means of raising individual immunity other than giving the products of metabolism produced by the meningococcus in culture. Any other method offered to increase the immunity will certainly be acceptable.

The comment of Drs. Vener and Parrish is the only dissenting opinion received up to the present time. However, I have received many letters from public health officials, pediatricians from medical schools including Harvard and Stanford, from this country and one was received from the chief health officer of Czechoslovakia, all commending the work and expressing a desire to give the toxin a clinical trial.

Although demands of the service have required that I take my tour on foreign duty at the present time, I am in a position to carry on further investigative work. The work begun at Leavenworth is being continued there by my former associates.

I should like to initiate a campaign to use the soluble toxin wherever outbreaks occur both in the civilian population and in the army. The use of the toxin in only half of the exposed groups over a period of several years in a large number of outbreaks should make decisive data available. This appears to be the next step in making use of an available control measure for meningococcic meningitis. Any suggestions as to a feasible method of carrying this out will be appreciated.

Drs. Vener and Parrish, it is believed, have not only misinterpreted our results but have arrived at their conclusions somewhat prematurely. Although all the evidence for immunization that we have at the present time is favorable, it is conceivable that the sequence of future events might alter this view. For that reason our only hope for progress in this work is to continue the clinical trial.

DWIGHT M. KUHNS, M.D., Ancon, Canal Zone.
Captain, M. C., United States Army.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

"NORMAL" ALCOHOL IN TISSUES—ABSORPTION OF ALCOHOL THROUGH SKIN

To the Editor:—1. I should like to know whether there is alcohol present normally in the blood and spinal fluid and if so to what level (milligrams per hundred cubic centimeters of fluid). 2. I should also like to know what level (milligrams per hundred cubic centimeters of blood and spinal fluid) is considered the point of occurrence of intoxication. 3. Has there ever been a case of alcoholic intoxication reported by absorption through the normal skin from local application? 4. What substances are most readily and rapidly absorbed through the normal skin by local application (without massage or other means of stimulating or increasing absorption)? How does alcohol compare with them in this respect? 5. Is individual sensitivity or tolerance a factor in the absorption of these substances, especially alcohol, through the skin normally, and if so to what extent?

B. H. BAYER, M.D., Houston, Texas.

ANSWER.—1. The amount of "normal alcohol" in body fluids is extremely small. Earlier investigators reported as much as 0.003 per cent, or 3 mg. per hundred cubic centimeters, but recent research indicates that most of the volatile reducing substance which was reported as alcohol is actually nonalcoholic in nature. Harger and Goss (*Am. J. Physiol.* **112**:374 [June] 1935) report the normal amount to be from 0 to 0.027 mg. per hundred grams. Spinal fluid analyses are not reported, but it is known that one or more hours after ingestion of alcohol the spinal fluid alcohol usually exceeds that of the blood by about 20 per cent.

2. When the blood alcohol reaches 0.02 per cent (20 mg. per hundred cubic centimeters) carefully controlled psychologic examinations usually demonstrate definite mental impairment. At a blood alcohol level of 0.07 per cent (70 mg. per hundred grams) or spinal fluid or urine level of about 10 per cent symptoms of intoxication are ordinarily observed, and this figure has been accepted by the Committee on Tests of Intoxication of the National Safety Council as prima facie evidence of intoxication. All carefully controlled observations of individuals whose blood alcohol has reached 0.15 per cent (150 mg. per hundred cubic centimeters) or whose urine or spinal fluid has reached 0.2 per cent have been deprived of some of that clearness of intellect and control of themselves which they would otherwise possess and they are therefore definitely under the influence of alcohol. The National Safety Council committee has therefore set these figures as incontrovertible evidence of intoxication.

3. Although fatal alcohol poisoning has been reported following the application of alcohol dressings on the skin of a burned individual (Frankel and Nicolai: *Deutsche Ztschr. f. gerichtl. Med.* **11**:134, 1928) no recorded case has been found of intoxication due to absorption of alcohol through the normal skin. However, the following experiment was performed in order

to answer the question regarding the possibility of absorption of alcohol through the normal skin: Two small children were given alcohol rubs lasting eight minutes. There was no possibility of inhalation of alcohol, since the subjects were properly attached to a basal metabolism machine. That definite absorption of alcohol occurred was demonstrated by a maximum alcohol concentration in the urine of 0.025 per cent.

4. David I. Macht (The Absorption of Drugs and Poisons Through the Skin and Mucous Membranes, THE JOURNAL, Feb. 5, 1938, p. 409) finds that the essential or volatile oils are readily absorbed through the intact skin and can be used as vehicles for the absorption of alkaloids and other drugs. Ethyl alcohol apparently compares unfavorably in its penetrability of the skin with the numerous substances tested by Macht.

5. No information is at hand regarding individual sensitivity or tolerance in the absorption of alcohol through the skin, but it is likely that the same factors apply to alcohol absorbed through the skin as for ingested alcohol.

POSSIBLE TOXIC EFFECT FROM METAL CLEANER

To the Editor:—Could you give me some idea of the composition and possible toxic symptoms arising from the use of a metal cleaner and paint remover put out by the Nielco Products Company of Detroit, under the serial number 22.

M.D., Indiana.

ANSWER.—The manager of the company mentioned was consulted in connection with this query. He states that item 22 of his company's products is strictly a metal cleaner and not a paint remover. Its ingredients are ethyl amyl ketone approximately 25 per cent, a sulfated lauryl alcohol approximately 25 per cent, and an undisclosed organic acid 50 per cent. The nature of this acid is a trade secret, but it may be noted that oleic acid or a similar fatty acid is frequently used in this type of cleanser. Of these substances, ethyl amyl ketone, because of its high boiling point (168 C.), is little likely to produce vapors. Although this substance may be highly toxic, it would be necessary to heat it in order to drive off high concentrations of vapors. Salts of lauryl sulfate are components of detergents such as Drene which do not cause precipitates with "hard" water. Of the major constituent, an organic acid, nothing beyond conjecture can be stated. From what is now known of this mixture, this cleanser as used in the ordinary course of metal polishing is likely to be the source of nothing more than a dermatitis, although the unknown acid prevents more certain statements. However, the prospects of its being a definite skin irritant are obvious. Potentially, the ethyl amyl ketone is the most injurious constituent.

CHRONIC CARBON MONOXIDE POISONING OR NEUROSIS

To the Editor:—A woman, aged 39, discovered a year ago that she and her room mate were exposed to carbon monoxide gas from an old furnace. They had occupied the same apartment for a number of years and felt sick periodically every winter. When finally carbon monoxide poisoning was suspected a quantitative blood test showed 20 per cent carbon monoxide in the blood. They moved immediately; in fact, they built a small house at the edge of town and installed electric and wood stoves. They avoid gas-heated houses, automobile rides and traffic. In spite of these exaggerated precautions they are almost continually ill, suffering from headache, anorexia, vomiting, amblyopia and general malaise. Nov. 4, 1937, the most careful physical examination, including blood and urine analyses and a Wassermann test failed to give any explanation. A quantitative blood analysis, however, showed 3 per cent carbon monoxide, and if it were not for this one would be tempted to label them as neurotic patients because of their phobia of smells and general complaints. I am at a loss to explain the consistent presence of carbon monoxide in the blood in an environment which is essentially free from carbon monoxide, and I know still less how to relieve them of their complaints, which are so disturbing that they may have to give up their positions. Oxygen inhalations give temporary relief. I am giving them vitamin C with the idea of increasing cell resistance. Any suggestions as to the treatment of these cases of real or apparent persistent carbon monoxide poisoning would be appreciated.

M.D., Oklahoma.

ANSWER.—It is difficult to determine from the facts given whether or not these women are suffering from chronic carbon monoxide poisoning. W. J. McConnell (Text-Book of Medicine, Cecil, Philadelphia, Fourth Edition, 1937) states that: "Chronic poisoning by CO is believed by many authors to be a clinical entity. It is certainly true that in many individuals long exposed to small amounts of CO there are such evidences of disease as persistent headache, malaise, and an ill-defined debility."

Henderson (J. A. M. A. **94**:179, Jan. 18, 1930) stated: "Less acute but more prolonged are the effects of repeated exposure to small amounts of carbon monoxide, such as a mechanic in an automobile repair shop breathes day after day, or a workman at a blast furnace or gas plant, or a cook working in a small badly ventilated kitchen with a defective gas stove. The results of such conditions are impairment of general health, nervousness, ill temper, and a condition similar to 'overtraining' in an athlete or to the 'air staleness' of an aviator who has made many high ascents.

"For such low grade chronic intoxication the only proper treatment, and all that is necessary, is the improvement of the conditions, especially the ventilation, under which the persons concerned live and work."

A percentage saturation of the blood to between 10 and 20 results in tightness across the forehead, possibly slight headache and dilatation of cutaneous blood vessels, while percentage of blood saturation between 20 and 30 results in headache and throbbing in the temples according to Sayers and Davenport (Public Health Bulletin No. 195, U. S. Public Health Service, 1930, p. 53).

According to these same authors percentage saturations below 20 per cent do not result in symptoms. Whether or not continued exposure which had resulted in 20 per cent saturation would have as prolonged an effect as indicated in the inquiry cannot be definitely stated. It would seem more likely, however, that if this symptomatology is resulting from carbon monoxide there is additional exposure to the gas in some concentration.

ASTHMATIC ATTACKS FROM COAL GAS

To the Editor:—One of my asthmatic patients has paroxysms every time he takes care of a coal water heater in the cellar. Is there a test which I can use in my office to detect a hypersensitiveness to coal gas or dust? I should appreciate information and technic concerning such a test. Is there any specific therapy for this type of asthma?

M.D., New York.

ANSWER.—Asthmatic attacks are commonly brought on by the fumes of coal gas. The general opinion is that this is a nonspecific effect. This may mean that the patient is specifically sensitive to something which has not been discovered; his actual attacks are precipitated by specific factors such as dust, infection and chemical fumes, among which coal gas plays an important part.

There is also the possibility that one may be specifically sensitive to coal gas or dust. This has not been sufficiently worked out. However, hypersensitivity to wood smoke has been described. For testing purposes one can use, for the scratch test method, preparations of wood smoke which are obtainable on the market.

It is further possible, in view of the history of attacks coming on while the patient is in the cellar, that something aside from coal gas or dust may be the causative factor. This is particularly true of fungi. Many allergic persons who have their attacks occur while in the cellar or basement owe the origin of these attacks to the inhalation of the fungus spores so commonly found in many basements.

STERILIZATION OF COCAINE HYDROCHLORIDE SOLUTIONS

To the Editor:—On two different occasions THE JOURNAL has published queries and minor notes on the sterilization of cocaine solutions. In one it says not to allow the temperature to go above 96 C., in the other that the solution should be placed in the sterilizer under 15 pounds pressure for fifteen minutes. I am informed that when under 15 pounds pressure for fifteen minutes the temperature is 234 F. This would cause a decomposition of the cocaine. I hope that you will bear with me as I desire answered in detail the two following questions so that I will feel that I am following the proper procedure in my institution: 1. I use 4 per cent cocaine solution for local anesthesia in cataract operations; what is the best way to prepare this solution so that I may feel assured that it is absolutely sterile? 2. I use 2 per cent cocaine in 1:8,000 epinephrine solution for local use in the nose. Please give in detail method of preparing a sterile solution of it.

M.D., Ohio.

ANSWER.—The A. M. A. Chemical Laboratory has written to a number of persons concerning the sterilization of cocaine hydrochloride solutions for use in the eye, nose or throat, and finds that this is not an easy question to answer. Apparently, boiling will give satisfactory results provided the solutions are not boiled for too long a time and of course the water must not be alkaline. The use of Seitz filters for sterilization of cocaine hydrochloride solutions has been recommended. This should be done only if the filter has been washed until the reaction of the washings is magnesia free. Washing with acid must be done before the filter is placed in the filtration apparatus and it should be thoroughly washed afterward with water.

A 1 per cent solution of cocaine hydrochloride in water gave a p_H value of 5.17 when freshly prepared and two months later gave a p_H value of 4.2 and showed negligible hydrolysis; a solution of the same strength but in 0.001 normal hydro-

chloric acid had a p_H value of 2.9 and was the same at the end of the period. A buffered solution hydrolyzed to the extent of 31 per cent in two months.

The pharmacist of the Presbyterian Hospital of Chicago advises that in the case of eye solutions he uses freshly redistilled water which is then boiled one minute. A discussion on the sterilization of easily decomposed chemicals appears in Martindale and Westcott's Extra Pharmacopeia, edition 16, volume I, page 288 and volume II, page 140.

Dean Edward Spease of the School of Pharmacy of Western Reserve University has furnished the list of references which follow. He states that 5 cc. ampules of 4 per cent cocaine hydrochloride are prepared in his institution by placing from 3.5 to 4 cc. in them and sterilizing for from fifteen to twenty minutes at 100 C. in a hot water bath, Kimball glass being used. Preparations of 4 and 10 per cent solutions were made by placing such solutions in bottles, glass stoppered, for use in laryngeal cocainization, which are not sterilized but with which there has been no difficulty. It is rare to have a solution older than one week or ten days.

Regnier, J., and David, R.: Effect of Heating on Anesthetic Power of Buffered Solutions of Cocaine Hydrochloride, *Bull. Sc. Pharm.* **40:** 650, 1933, through *Quart. J. Pharm. & Pharmacol.* **7:** 139, 1934.

One per cent solutions of cocaine hydrochloride when sterilized in an autoclave at 120 C. for fifteen minutes with phosphate buffers lose their anesthetic powers entirely if neutral and lose the greater part of their anesthetic powers if acid. If buffered weakly with calcium carbonate or magnesium carbonate near neutrality, activity is wholly retained with magnesium carbonate and 70 per cent retained with calcium carbonate. On sterilization, these buffered solutions have a p_H of about 3.8.

Regnier, J., and David, R.: Effect of Hydrogen Ion Concentration and Buffer Action on Physiologic Action of Cocaine Hydrochloride, *Bull. Sc. Pharm.* **41:** 321, 1934.

Solutions of cocaine hydrochloride buffered with sodium acid phosphate and disodium phosphate show before sterilization an increase of physiologic activity compared with aqueous solutions. Activity increases with alkalinity. When heated at 100 C. for one hour, the solution becomes acid and finally reaches a p_H of 4. Heating results in almost complete loss of activity.

A 1 per cent solution of cocaine hydrochloride of p_H 4.4 and buffered with acetic acid and sodium acetate shows, before heating, activity equivalent to a 1.5 per cent solution in water, and, after heating, activity is doubled. After storage, activity is equivalent to a 2.4 per cent solution.

Dietzel: Stability of Alkaloids, *Pharm. Zentralbl.* **75:** 469 (No. 30), 1934, through *Squibb Abstracts* 7, 1934.

The p_H for the maximum stability of cocaine solutions is 3.5.

Regnier, J., and David, R.: Effect of Sterilization on the Stability of Solutions of Cocaine Hydrochloride, *Bull. Sc. Pharm.* **41:** 468, 547, 595, 1934, through *Quart. J. Pharm. & Pharmacol.* **8:** 571, 1935.

Strongly buffered neutral or alkaline solutions rapidly lose anesthetic power on heating at 110 C. Solutions of p_H about 4 offer most resistance to loss of anesthetic power.

Schou, S. A., and Heim, E.: Sterilization of Cocaine Solution, *Pharm. Act. Helv.* **10:** 31, 1935, through *Quart. J. Pharm. & Pharmacol.* **8:** 287, 1935.

Buffer of p_H over 4 accelerates hydrolysis. Solutions of the hydrochloride may be sterilized for thirty minutes at 100 C. If 1 cc. of tenth normal hydrochloride acid per hundred cubic centimeters of solution is added, it may be sterilized for thirty minutes at 120 C.

Tiffeneau: Stabilization of Cocaine Hydrochloride Solutions, *Un. pharm. Paris* **75:** 195, 1934, through *Quart. J. Pharm. & Pharmacol.* **7:** 736, 1934.

Solution of cocaine hydrochloride, p_H 4, with monosodium phosphate buffer, resists heating badly.

Solution of p_H 4.4 with acetic acid and sodium acetate buffer resists heat, and the anesthetic power is increased.

URTICARIA PIGMENTOSA

To the Editor:—A girl baby, aged 3 months, had urticaria pigmentosa, and the condition has remained stationary up to the age of 2 years. Please suggest treatment and prognosis and possible etiology.

J. GILBERT EBLEN, M.D., Knoxville, Tenn.

ANSWER.—The Suttons in their book published in 1935 define urticaria pigmentosa as a chronic inflammatory disease of the skin characterized by lesions which resemble wheals in many respects but the majority of which persist and ultimately become pigmented. The condition is comparatively rare in the United States but is more common in Great Britain. Several hundred cases have been recorded from various parts of the world. It usually begins in early infancy with wheals, papules and nodules, resembling ordinary urticaria at first. The lesions appear all over the body, usually persist, and in a week or two become pigmented. They may coalesce. The lesions are slightly elevated, with firm and well defined bases and chamois color or brown. Vesiculation occurs occasionally. New lesions occur from time to time; older lesions subside and sometimes leave atrophic spots or even scars. Itching is usually severe, and itching and pigmentation may persist after the lesions disappear. The duration is indefinite, with periods of remission. One type is microscopically free from characteristic mast cells.

Little is known regarding the etiology. It usually begins in infancy, although it may start after the age of 20 or even 30. Stelwagon has expressed his belief that urticaria pigmentosa is related to urticaria, the subsequent peculiarities being a result of secondary changes. Parkes Weber is of the opinion that urticaria pigmentosa is related to telangiectasia. Finnerud found 53.3 per cent of the patients male and 46.7 per cent female; 46.1 per cent began within the first year, 67.1 per cent before the thirteenth year, and 32.9 per cent among adults; 61.7 per cent were macular, 7.8 per cent nodular and 30.5 per cent maculonodular; in eight cases vesicles and bullae were present.

The lesions resemble ordinary urticaria but show enormous infiltration of mast cells instead of the usual collection of leukocytes. Hannay and Mount state that there is no reason to differentiate the condition from ordinary urticaria; they believe it is urticaria plus pigmentation.

It is differentiated from urticaria by the early onset, persistence and pigmentation; from xanthoma by the evanescent character of some of the lesions, intense itching and usual youth of the patient. It usually tends to disappear as puberty is reached. There are many remedies but none are very effective. Pilocarpine and atropine are probably the most useful. Antipruritics are given for relief of the itching. Michael found that three of four cases improved under x-ray treatment.

In the last few years many more case reports have been published, among them the case of Sézary, Caroli and Horowitz, in which no pigmentation was present yet mast cells infiltrated the cutis. Weber and Rast quote several cases in adults and describe one new case in an adult. The adult cases seem to persist for many years and no very efficacious treatment has been found.

LIPOMA AND LIPURIA

To the Editor:—Is it probable that a superficially growing lipoma would absorb, producing a lipuria?

M.D., California.

ANSWER.—It is unlikely that a superficial lipoma would produce lipuria. It seems all the more unlikely in that lipuria has not been reported in more extensive diseases of generalized subcutaneous fat deposits, such as occur in relapsing febrile nodular nonsuppurative panniculitis.

THUMB SUCKING AND NAIL BITING

To the Editor:—I would appreciate any information regarding the safety and efficacy of thumb sucking devices. There is an appliance called "Stop" made by the Corrective Guild in Los Angeles, about which I should like information. If there is any other appliance for thumb sucking or finger nail biting that you think well of, please let me know.

SIDNEY TRATTNER, M.D., Richmond, Va.

ANSWER.—Thumb sucking is an infantile habit and in the early months of life seems to be normal and innocent. In many instances the children stop voluntarily before the school age. It is only when the habit is persistent and intensive that dental malocclusion may occur.

None of the many devices for preventing the habit, or anointing with bitter or distasteful drugs, seem to effect a permanent cure. One should assume that the young child does not know that the habit is objectionable. He should be encouraged to play with other children and, if he is found indulging in the habit, his attention should be diverted.

Nail biting usually indicates a higher state of nervous tension and is more difficult to control.

It is doubtful whether any of the mechanical devices accomplish the purpose for which they are intended. Parents and even physicians are sometimes more concerned about the habit than is called for.

FLUORINE POISONING

To the Editor:—Please send me the best treatment for fluorine gas poisoning.

M.D., New Jersey.

ANSWER.—There is so little experience on either acute or chronic fluorine poisoning that statements as to treatment should be made and accepted with caution. Fluorine compounds may exert a local action on the skin or may be ingested and followed by acute or chronic poisoning; some gases, vapors or dusty compounds may be inhaled. Apart from suicidal or accidental intakes of fluorine compounds, acute episodes chiefly are associated with fluorine entry by inhalation. As little as 0.2 mg. of fluorine per kilogram of body weight may lead to injury. Acute episodes following inhalation are dominated by pulmonary edema. The chronic state is characterized by overgrowth of bone, calcification of ligaments and bony fragility. For the acute states associated with fluorine inhalation, the following treatment may be indicated: oxygen inhalation, bronchial sedatives to allay violent coughing, the use of bronchial antispasmodics when bronchial asthma appears, the intravenous administration of calcium gluconate, as recommended

by McNally. In general, symptomatic treatment is indicated. In less acute cases, constipation or obstipation may call for treatment. In some instances severe vomiting may appear and call for symptomatic care. No established treatment exists for the stiffness of the body due to bony and ligamentous changes, but it appears that on the gradual elimination of fluorine considerable reduction takes place in the osseous overgrowth. On occasion as much as sixty times the normal content of fluorine in bony tissues may exist. Additional information may be found in the following:

Roholm, Kaj: Fluorine Intoxication, with a Review of the Literature and Some Experimental Toxicity, London, H. K. Lewis & Co., 1937.

Roholm, Kaj: The Fog Disaster in the Meuse Valley, 1930: A Fluorine Intoxication, *J. Indust. Hyg. & Toxicol.* **19:** 126 (March) 1937.

Machle, Willard; Thamann, Frederick; Kitzmiller, Karl, and Cholak, Jacob: The Effects of Inhalation of Hydrogen Fluoride: I. Response Following Exposure to High Concentrations, *J. Indust. Hyg.* **16:** 129 (March) 1934.

Machle, Willard, and Kitzmiller, Karl: The Effects of the Inhalation of Hydrogen Fluoride: II. The Response Following Exposure to Low Concentrations, *J. Indust. Hyg.* **17:** 223 (Sept.) 1935.

Machle, Willard, and Scott, E. W.: The Effects of the Inhalation of Hydrogen Fluoride: III. Fluorine Storage Following Exposure to Sublethal Concentrations, *J. Indust. Hyg.* **17:** 230 (Sept.) 1935.

Cirla, P.: The Phosphorus Content of Blood and of Bone in Various Types of Experimental Poisoning: Lead, Mercury, Chromium, Phosphorus, Strontium and Flourine, *Med. d. lavoro* **28:** 44 (Feb.) 1937.

Roholm, Kaj: Acute Fluorine Poisoning, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **27:** 174, 1936.

Volter, S. V.; Ablina, T. N., and Kremneva, S. N.: Toxic Effect of Flourine Compounds in the Phosphate Fertilizer Industry, *Gigiena truda i tek. bezopasnosti* **32,** No. 5, 1935.

Bishop, P. A.: Bone Changes in Chronic Fluorine Intoxication, *Am. J. Roentgenol.* **35:** 577 (May) 1936.

Roholm, Kaj.: Fluorine Poisoning in Cryolite Workers, *Arch. f. Gewerbepath. u. Gewerbehyg.* **7:** 255, 1936.

ALLERGIC BLEPHARITIS

To the Editor:—What treatment is advisable for allergic blepharitis? The patients have swelling and redness of the eyelids with intense itching and burning of the eyes, but the conjunctiva is usually clear. Please outline a palliative treatment for this condition, leaving out allergic testing.

EARL H. BROWN, M.D., Tucson, Ariz.

ANSWER.—Allergic blepharitis is certainly an unusual condition if it ever occurs. The symptoms of itching and burning with recurrent swelling are not enough to form the basis of a diagnosis of an allergic condition. Symptoms such as those described are usually relieved with ice during acute attacks of swelling, while the inflammation of the lids is best treated with zinc oxide powder or a 3 per cent zinc oxide ointment in hydrous wool fat. It is necessary, of course, to remove all possible sources of irritation such as cosmetics, hair tonics, hair dyes and especially lash dyes. It is usually possible, by bacteriologic examination and examination for eosinophils, to come to a fairly definite conclusion as to whether the condition is on an infectious or an allergic basis, which is, of course, of utmost importance for any kind of rational treatment.

ELECTROSTERILIZATION OF ROOT CANALS

To the Editor:—Could you give me any information concerning ionization treatment? I am particularly interested with regard to its use for the treatment for dead teeth.

FRED E. CARPENTER, M.D., Newton, Iowa.

ANSWER.—Ionization, or electrosterilization as it has sometimes been called, was introduced in dentistry in the early years of the present century. It created a great wave of enthusiasm and machines were manufactured by the hundreds by dental supply houses but it almost immediately faded out. It is probable that the reason for such a prompt and complete failure was that most of the members of the dental profession were not sufficiently trained in chemistry, biology and physics to make intelligent use of the apparatus. Bad effects were frequent and rather serious in some cases and the whole process went into disrepute. A few men continued, however, and have used the method successfully for twenty-five years or more.

The method depends on the separation of molecules into their ions; positive ions move in an electric current to the negative pole and negative ions move to the positive pole. By this method antiseptic and germicidal chemicals can be carried into the tissues to reach areas of infection not accessible from the surface. It is clear that such a method requires a good background in chemistry, physics and biology for its successful application. Chemicals that will destroy bacteria have a more or less deleterious effect on tissue cells and it is quite easy to destroy not only the bacteria but the tissue cells, making the situation worse rather than better. The recent method employed in treating such conditions as infections around the apexes of tooth roots has tended strongly in the direction of removing the source of bacterial infection and leaving the tissues to fight out the battle with the bacteria by means of their own defense mechanism. It is, however, probably possible by intelligent use of this method to kill bacteria in the tissues and at the same time stimulate the tissues and their defense mechanisms.

Dr. H. B. Johnston of Atlanta, Ga., has been using the method for a long time. He presented a clinic at the recent midwinter meeting of the Chicago Dental Society and he has a paper on the improved status of the pulpless tooth in the March 1938 issue of the *Journal of the American Dental Association,* volume 25, page 429. This article is chiefly a discussion on focal infection but refers to electrosterilization. A large amount of material has been written on this subject and reference should be made to two textbooks, one by Ernest Sturridge, Dental Electro-Therapeutics, Philadelphia, Lea & Febiger, 1914, and one by Herman Prinz, Dental Materia Medica and Therapeutics, St. Louis, C. V. Mosby Company, 1917, and to the following list of journal articles:

Prinz, Hermann: Electrosterilization of Root Canals, *Cosmos* **59:** 373, 1917.

Sturridge, Ernest: The Electrotherapeutic Action of Certain Ions, *Cosmos* **59:** 793, 1917.

Sturridge, Ernest: Ionization in Root Canal Therapy, *Brit. Dent. J.,* 1923, p. 1420.

Rhein, M. L.; Krasnow, F., and Gies, W. J.: A Prolonged Study of the Electrolytic Treatment of Dental Focal Infection, *Cosmos,* 1926, p. 971.

Prinz, Hermann: Electrosterilization of Root Canals, *Cosmos,* 1917, p. 373.

Johnston, H. J.: Destruction of Apical Infection, *J. Dent. Res.* **4:** 109, 1922.

Badecker, C. F.: The Ionization of Septic Roots, *Cosmos* **69:** 1157, 1927.

Grossman, L. I., and Appleton, J. L. T.: Experimental and Applied Studies in Electrosterilization, *Cosmos* **73:** 147, 1931.

Hospers, John. Electromedication in Root Canal Therapy, *Dental Digest* **41:** 117, 1935.

Grossman, L. I., and Prinz, Hermann: A Comparative Study of Root Canal Therapy with (1) Camphorated Chlorphenol and with (2) Electrosterilization, *Cosmos* **74:** 324, 1932.

Johnston, H. B.: Clinical Results in Periapical Sterilization, *J. Am. Dent. A.,* 1924, p. 1170.

DIAGNOSIS OF PENILE ULCERS

To the Editor:—During the last four months I have been treating for scrofula a Negro aged 45. His general health had apparently been below par for several years because of phagedena of the penis. When I first saw him, the prepuce presented a mouse-eaten, jagged appearance with a copious thin reddish gray discharge and had partly sloughed away. Verrucae were also present on the ragged edges of the prepuce. The tissues of the penis were inflamed, red, swollen, and firm to the touch. There were numerous small openings in the shaft of the penis from which a considerable amount of pus could be expressed. Microscopic examination of the specimen slides of the pus revealed two strains of staphylococci. At present the prepuce, glans penis and a small portion of the distal extremity of the shaft of the penis have sloughed away and the ulcerated remaining tissues are bloody when a gauze dressing is removed or when the tissues are lightly touched with a gauze sponge. Previous reports indicate that the patient had a positive blood Wassermann test and an unknown amount of antisyphilitic treatment in 1932 following a venereal infection which was at that time diagnosed as chancroid. The treatment has consisted of cleansing the parts with antiseptic solutions, hot fomentations, applications of iodoform powders, iodoform gauze and chemical cauterization. Neoarsphenamine has been administered intravenously on the theory that the condition might be due to a gumma. A blood Wassermann test and spinal fluid examination were negative at the time the treatment was instituted. So far the condition has resisted all treatment and has shown no tendency to heal. What is your opinion as to etiology, diagnosis, treatment and prognosis? Please give full information concerning the disease of venereal phagedena and also references to standard textbooks on this subject.

M.D., Virginia.

ANSWER.—Gumma can be ruled out because of the nature of the ulcers and the infiltrate described and because of the failure to heal after antisyphilitic treatment. Tuberculosis colliquativa (scrophuloderma), chancroid, granuloma inguinale, venereal lymphogranuloma and actinomycosis or some similar fungous disease should be considered. There may be multiple infection.

Tuberculosis may sometimes be proved by direct examination of smears from the pus. Fungi may also be found in this way. If this fails, a biopsy should be taken under precautions against introducing any other organisms than those already present and part of it inoculated into guinea pigs, smears from the base of the biopsy examined for tubercle bacilli and Donovan bodies and the rest sectioned for microscopic and bacteriologic study. General examination for tuberculosis, including roentgen studies and tuberculin tests, should be made.

Granuloma inguinale is suggested by the excessive granulations, bleeding on removal of dressings. The Donovan bodies are seen best when stained with Wright stain, as oval, apparently encapsulated bodies, intracellular or extracellular, sometimes bacillus-like, in other places like diplococci. They measure from 1 to 3 microns.

Venereal lymphogranuloma is tested for by the Frei test, injection of 0.1 cc. of Frei antigen intracutaneously on the flexor surface of the forearm. A papule 0.5 cm. in diameter or larger within two days indicates a positive reaction.

Chancroid can sometimes be proved by finding the streptobacillus of Ducrey in smears from beneath the overhanging edge of the ulcer. A skin test with a vaccine produced in Europe, called "dmelcos," is made by intracutaneous injection of 0.1 cc. A papule 0.5 cm. in diameter within two days indicates a positive reaction. Like the Frei test, this may occur in persons who have been infected years before and show no signs of the disease. Cole and Levin (The Intradermal Reaction for Chancroids with Chancroidal Bubo Pus, THE JOURNAL, Dec. 21, 1935, p. 2040), because of the difficulty of obtaining dmelcos vaccine, made a vaccine from the pus of chancroidal buboes. The pus was diluted with four parts of physiologic solution of sodium chloride and heated at 60 C. for two hours the first day and one hour the second day and then cultured for sterility. It is used in the same way as the dmelcos vaccine.

Actinomycosis or other fungus, if not found in the direct smear, either stained or examined fresh in potassium hydroxide solution, may be seen in the microscopic section, or the pus can be inoculated on some sugar medium, preferably Sabouraud's.

The prognosis, no matter which of the diseases mentioned is responsible, is not good for a patient who has had the trouble for several years and is in poor condition.

Treatment must consist first in efforts to improve the patient's general condition and to raise resistance. General exposures to ultraviolet rays may be of assistance, combined with rest in bed and good food. Roentgen rays in divided doses to the affected parts may help in most of the conditions mentioned. In addition to the local treatment for chancroids, some patients have been benefited by intravenous injections of the vaccine used for diagnosis. From 1 to 2.5 cc. has been given every second or third day, causing a febrile reaction. The stomach must be empty when the injection is given.

If lymphopathia venereum or granuloma inguinale is found, intravenous injections of 1 per cent antimony and potassium tartrate solution, beginning with a dose of 3 cc. diluted to 10 cc. with physiologic solution of sodium chloride should be given. The dose may be increased in successive injections by increasing the amount of the antimony and potassium tartrate solution and decreasing the amount of the diluent until undiluted 1 per cent antimony and potassium tartrate solution is used in a 10 cc. dose. These injections are given twice a week. The urine must be watched for albumin or casts, and some nausea and headache must be expected after the injections. Fuadin (proprietary name of the Winthrop Chemical Company for sodium antimony III biscatechol disulfonate of sodium) is less toxic and at least equally effective. Benefit has been reported from repeated injection of the Frei vaccine in the treatment of venereal lymphogranuloma and intravenous injections of compound solution of iodine have been beneficial. Surgery is of importance in the treatment of both diseases.

Actinomycosis is treated by large doses of iodides by mouth or intravenously and by roentgen rays locally. Thymol applied in 10 per cent solution in olive oil locally in the sinuses and crystalline thymol from 1 to 1.5 Gm. in capsule by mouth once a day have cleared up several cases (Myers, H. B.: Thymol Therapy in Actinomycosis, THE JOURNAL, May 29, 1937, p. 1875). Surgery may be a valuable aid here also.

A more thorough discussion of these diseases may be found in Cabot's Modern Urology, third edition, Philadelphia, Lea & Febiger, 1936, volume 1, page 217.

EFFECT OF STORING SERUMS ON WASSERMANN REACTION

To the Editor:—Are there two different kinds of blood serums with respect to the speed of reaction to the Wassermann test? Is there a blood serum which works slowly and if allowed to stand will give a negative test but when read early will give a positive reaction?

J. W. HOPKINS, M.D., Glendale, Calif.

ANSWER.—Serums giving definitely positive or definitely negative serologic reactions undergo little or no change on standing one or more days at ice box temperature. Serums giving weak or borderline serologic reactions may undergo such changes as to give either stronger or weaker reactions after standing one or more days in the cold. Prolonged standing (a week or more) even at ice box temperature will generally not affect negative serums but is likely to cause strongly positive serums to give weaker serologic reactions. The reason for these changes in serum reactions is not known.

Medical Examinations and Licensure

COMING EXAMINATIONS

STATE AND TERRITORIAL BOARDS

Examinations of state and territorial boards were published in THE JOURNAL, July 9, page 193.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* Examinations will be held in all centers where there is a Class A medical school and five or more candidates who wish to write the examination, Sept. 12-14. Ex. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

SPECIAL BOARDS

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: St. Louis, Nov. 11-12 *if the number of candidates warrants it.* Applications of Class B candidates should be filed by Sept. 1 and of Class A by Oct. 1. Sec., Dr. C. Guy Lane, 416 Marlboro St., Boston.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written examination* will be held at various centers of the United States and Canada, Oct. 17. *Final date for filing applications is Sept. 1.* Chairman, Dr. Walter L. Bierring, 406 Sixth Ave., Suite 1210, Des Moines, Iowa.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written examination for Group B candidates* will be held in various states of this country and Canada, Nov. 5. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh (6).

AMERICAN BOARD OF OPHTHALMOLOGY: New York, Oct. 7, and Washington, D. C., Oct. 8. *All applications should be filed immediately and case reports, in duplicate, must be filed not later than sixty days before the date of examination.* Sec., Dr. John Green, 3720 Washington Blvd., St. Louis, Mo.

AMERICAN BOARD OF OTOLARYNGOLOGY: Washington, D. C., Oct. 7-8. Sec., Dr. W. P. Wherry, 1500 Medical Arts Bldg., Omaha.

AMERICAN BOARD OF PEDIATRICS: Detroit, October 26; Rochester, N. Y., November 13; and Oklahoma City, November 15. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

AMERICAN BOARD OF RADIOLOGY: Atlantic City, N. J., Sept. 15-18. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave. S.W., Rochester, Minn.

Colorado April Report

Dr. Harvey W. Snyder, secretary, Colorado State Board of Medical Examiners, reports the written examination held at Denver, April 6-8, 1938. The examination covered 8 subjects and included 165 questions. An average of 75 per cent was required to pass. Ten candidates were examined, nine of whom passed and one failed. Six physicians were licensed by endorsement on April 5. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Creighton University School of Medicine		(1937)	83
University of Oklahoma School of Medicine		(1937)	84, 85
Julius-Maximilians-Universität Medizinische Fakultät, Würzburg		(1935)	86
Philipps-Universität Medizinische Fakultät, Marburg		(1934)	85.5
Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest		(1937)	84.5
Osteopaths *		80.5,	81, 84

	FAILED	Per Cent
Osteopath *		74.4

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
Rush Medical College		(1927), (1936)	Illinois
University of Illinois College of Medicine		(1936)	Illinois
University of Nebraska College of Medicine		(1932) (1934)	Nebraska, Wyoming
University of Oregon Medical School		(1934)	California

* Examined in medicine and surgery.

National Board of Medical Examiners

The National Board of Medical Examiners reports that its certificate was awarded to sixty-six applicants who were successful in the examinations in part III held at Chicago and New York in January 1938. The following schools were represented:

School	PASSED	Year Grad.	Number Passed
College of Medical Evangelists		(1937)	1
Yale University School of Medicine		(1935), (1936)	2
Georgetown University School of Medicine		(1935), (1936, 3)	4
Loyola University School of Medicine		(1937)	1
Northwestern University Medical School		(1932), (1937, 3)	4
Rush Medical College		(1937, 2)	2
School of Med. of the Division of Biological Sciences		(1937)	1
University of Illinois College of Medicine		(1937)	1
University of Louisville School of Medicine		(1936, 3)	3
Boston University School of Medicine		(1936)	1
Harvard University Medical School		(1934), (1935), (1936)	3
Tufts College Medical School		(1936, 2)	2
University of Michigan Medical School		(1934), (1935)	2
Wayne University College of Medicine		(1935)	1
St. Louis University School of Medicine		(1935)	1
Creighton University School of Medicine		(1936)	1

Columbia Univ. College of Physicians and Surgeons...(1933)	1
Cornell University Medical College.....(1934), (1936, 4)	5
Long Island College of Medicine.....(1935), (1936)	2
New York Medical College and Flower Hospital.....(1936, 12)	12
New York University College of Medicine...(1935), (1936, 3)	4
University of Buffalo School of Medicine.....(1936)	1
University of Cincinnati College of Medicine.....(1936)	1
Woman's Medical College of Pennsylvania.....(1930), (1935)	2
Baylor University College of Medicine.....(1936)	1
University of Vermont College of Medicine.....(1936)	1
Medical College of Virginia.....(1930)	1
Marquette University School of Medicine.....(1931)	1
Medizinische Fakultät der Universität Wien.....(1936)	1
American University of Beirut School of Medicine.....(1934)	1
Universität Zürich Medizinische Fakultät.....(1936)	1
Université de Genève Faculté de Médecine.....(1936)	1

Book Notices

A Symposium on Cancer. Addresses Given at an Institute on Cancer Conducted by the Medical School of the University of Wisconsin. Cloth. Price, $3. Pp. 202, with illustrations. Madison: University of Wisconsin Press, 1938.

In this short book are collected a series of seventeen papers outlining the paths which investigations on cancer have been taking. The busy practitioner, as well as others who have heard rumors of the recent rapid advances of studies in the nature and etiology of cancer and who wish to know about them, can read this volume with profit. Many aspects of the constitutional, genetic, endocrine and virus nature of cancer genesis are well presented, as well as the nature of the cancer cell itself, together with other problems in cancer. Kreyberg begins the symposium by speaking on the genetic and constitutional aspects of spontaneous and induced tumors. Little, in a chapter on the influence of intrinsic factors in the development of tumors in mice, shows the importance and complexity of such factors. Macklin states that the familial incidence of cancer points to an inherited factor, which is difficult to detect because of the complexities of genetic transmission and because different types of cancer may have different modes of transmission. Allen describes the effects of ovarian hormones in producing atypical growths and malignant tumors in the genital tissues as well as others. Andervont reviews the subject of the chemical carcinogens, the relation of chemical structure to cancerogenic activity, the fundamental method of action, and the types of tumors produced. Macklin discusses the factor of chronic irritation in the genesis of cancer and points out genuine errors in commonly held ideas. Ewing, in discussing cancer as a public health problem, summarizes the progress that has been made and points out the necessity for an aware public and a well trained medical organization. Fialla discusses the influence of wavelength on the histologic action of radiation. Coutard, in a chapter on the tissue reaction to irradiation, expounds his view on periodicity and radiosensitivity. Lewis contributes an absorbing chapter on the evidence obtained from tissue cultures of cancer cells, showing that they are new races of permanently altered cells. Reimann discusses the biology of the cancer cell. Murphy evaluates the evidence for a virus etiology of malignancy and points out that this is untenable from the evidence now available. Ewing discusses the biopsy, including methods, and indications for its use in many locations. He emphasizes aspiration biopsy. Andervont reviews the effects of bacterial products on the growth of malignant tumors. Novak considers the status of the early recognition, clinically and pathologically, and the treatment of cervical cancer, evaluating the microscopic changes that may lead to cancer. Coutard discusses the radiologic treatment of breast cancer. Kreyberg, in the concluding chapter, gives some results showing the influence of extrinsic factors on the development of induced tumors in genetically homogenous strains of mice.

Opium Addicts and Addictions. By John A. Hawkins, M.D. Cloth. Price, $2.50. Pp. 156. Boston: Bruce Humphries, Inc., 1937.

This book, without index or bibliography, is written in semipopular style. It may be considered as a print of the individual experiences of the author with drug addicts and addiction. His last chapter is a dramatic appeal to practitioners generally that there are dangers in the uses of opium or its derivatives in the legitimate practice of medicine. He discusses in general the indispensable uses of opium, the ill advised prescribing, and also the prescribing by physicians in direct contravention of the law in an effort to satisfy the craving of addicts. He deplores the latter situation and advocates complete isolation of all addicts. He thinks that a state jurisdiction is not capable of accomplishing this and advocates that the federal government assume such a responsibility. The latter suggestion may be open to some question in view of the fact that the police power exercised over individuals aside from those who commit offenses against the law is exceedingly limited.

His own experience in connection with the treatment of a protracted, painful illness, during which time he became tolerant and dependent on morphine, leads him to warn other practitioners against the careless and unnecessary use of powerful drugs capable of causing addiction and to assure them that the condition of addiction, though well established and of long standing, is curable if proper methods are employed and that permanence may be reasonably hoped for in many cases. The author does not share the traditional opinion that, "once an addict, always an addict." In his own case, however, he never encountered that emotional insecurity which is so common among drug addicts, an attitude of mind which is aided and abetted in part by the traditional outlook toward them and in part also by the innate tendency of the personality involved, since many addicts have shown long before they embraced the use of drugs an emotional insecurity toward situations of life. The author during his addiction never felt deserted, hopeless or ashamed. Such a mental attitude is in part responsible for his rehabilitation.

The fore part of the book contains a brief comment on the vernacular of drug addicts. In the foreword he indicates a wide experience in the treatment and management of these unfortunate persons while they have been incarcerated in penal institutions, and also from the standpoint of ambulatory care. He condemns the practice of ambulatory treatment for drug addiction, as he thinks it unpractical. He says in his foreword, "If what is contained in these pages shall have the effect of making some fellow-practitioner a little more careful in the administration of habit-forming drugs to patients who may become addicted to them, or if it shall cause some of them to be more tolerant with those already enslaved to drugs, then I shall know that my suffering has not been in vain."

The first chapter deals with an elementary dissertation on the pharmacology of opium and its effects, the second with the subject of tolerance, and the third with those who have become addicted, illustrated by case histories, the type of individual who becomes addicted, and the degradation which follows. By way of illustration the cases cited are largely of persons showing warped and distorted personalities even before they embraced the use of drugs, but by contrast he presents a case in which the emotional background and character are of such a nature that rehabilitation and restoration to a normal existence take place. He describes in some detail the symptoms seen when opium is abruptly and suddenly withdrawn and the treatment of that aspect of addiction. He discusses in a general way the need for community placement and supervision and the need for occupation in the scheme of rehabilitation. He does not touch on the psychiatric aspects of the problem or on the necessity for undertaking reintegration of the personality concerned.

L'exploration radiologique post-opératoire de la voie biliaire principale. Par B. Desplas, P. Moulonguet et P. Malgras. Paper. Price, 40 francs. Pp. 120, with 40 illustrations. Paris: Masson & Cie, 1938.

This is undoubtedly the most complete exposition of the postoperative radiologic examination of the biliary ducts, the arborization of the biliary tracts and even the duct of Wirsung. These Frenchmen have used lipiodol for opaque injections while some American experimenters have chosen hippuran because the heavy oil seemed to mask the shadows of small stones remaining in the common duct. The first intimation of the possibility of studying the contrary postoperative complications of gallbladder surgery originated with the accidental filling of the biliary tracts during a barium sulfate meal study by Beall and Jagoda of Fort Worth, Texas. This was followed promptly by American and French reports in 1922. Since 1934 there have been many reports of experimental and clinical studies which are completely catalogued in this monograph. The illustrations are accompanied by diagrams that facilitate understanding. The wealth of clinical material on retained calculi,

obstructions from retained clots or cicatricial conditions, chronic pancreatitis and cancer of the pancreas, cysts of the pancreas and biliary fistulas makes the small monograph quite valuable. American sources of such studies are relatively rare. Probably the most complete are those of Hicken, Best and Hunt of Omaha early in 1936. As this roentgen procedure is not difficult, we may look forward to its adoption into the routine of those examinations which may be useful in the postoperative study of gallbladder complications.

Pneumonia and Serum Therapy. By Frederick T. Lord, M.D., Member of the Board of Consultation, Massachusetts General Hospital, and Roderick Heffron, M.D. Revised edition of Lobar Pneumonia and Serum Therapy. Cloth. Price, $1. Pp. 148, with 10 illustrations. New York: Commonwealth Fund; London: Oxford University Press, 1938.

This little book contains an admirable description of the applications of specific serum to the therapy of pneumococcic pneumonia. In it are discussed the factors influencing recovery, clinical diagnosis, types of pneumococcic infection and use of serum, the precautions and complications of serum administration, the dosage, and an excellent summary of the effects of serum treatment on the death rate. While it does not aim to discuss all phases of the diagnosis and treatment, it furnishes a reliable analysis of the present status of serum therapy. The important points of technic are well considered, and the book should be an invaluable aid to those at any time treating pneumococcic pneumonia.

Trichinosis: Report of an Outbreak of 25 Cases. By Hyman I. Vener, M.D., C.P.H., Assistant Epidemiologist, and George M. Stevens, M.D., Epidemiologist. Los Angeles City Health Department, Hon. Frank L. Shaw, Mayor. George Parrish, M.D., Health Officer. Los Angeles City Board of Health Commissioners Bulletin No. 33. Paper. Pp. 17. Los Angeles, 1938.

This brochure is a report of an outbreak of twenty-five cases of trichinosis occurring in eight households in Los Angeles. The infection was apparently transmitted by eating lack-schinken, a smoked raw ham which resembles Canadian bacon, the suspected product having been peddled from house to house. All cases were confirmed by definite eosinophilia and in many instances by positive cutaneous tests. The symptoms were mild, which fact apparently served to produce some initial confusion in diagnosis. The report concludes with the authors' belief that the cutaneous test serves as a valuable adjunct in diagnosis.

Viruskrankheiten des Menschen: Ihre Erreger und ihre Bekämpfung. Von Dr. med. Richard Bieling, a. o. Professor für Hygiene und Immunitätswissenschaft an der Philipps-Universität, Marburg/L. Paper. Price, 4.80 marks. Pp. 114. Leipzig: Johann Ambrosius Barth, 1938.

This brochure on virus diseases concerns itself essentially with the virus diseases in man. There is a summary of virus diseases in animals and a correlation is made with the disease in animal as it may affect man; for example, foot and mouth disease in animals and its correlation in man. Another correlation is made between swine and human influenza. As a textbook this work cannot be used by students in bacteriology or those interested in virus diseases except as an outline of the subject of virus diseases and a short discussion on immunity. The author has attempted to give a review of the subject of virus diseases and has included a brief bibliography at the end of each chapter. The brief review of the literature is brought down to the year 1937.

Les explorations fonctionnelles. Par Noel Fiessinger, professeur de pathologie expérimentale et comparée à la Faculté de médecine de Paris. Paper. Price, 70 francs. Pp. 430, with 65 illustrations. Paris: Masson & Cie, 1937.

This volume is not primarily a laboratory manual. Rather it is a combination of physiology and clinical laboratory diagnosis. Methods of estimating the functional capacities of the various organs are presented, with a correlation between the function in health and in disease. The limitations and applicabilities of each method are well discussed. The scope of the book is wide, embracing consideration of the central nervous system, lungs, heart, gastrointestinal tract, liver, spleen, pancreas, kidneys, endocrine glands, blood and reticulo-endothelial system. Because of the wide field covered, the separate discussions are often brief. This brevity is particularly noticeable in the discussion of the blood, the electrocardiogram, the cerebrospinal fluid and the endocrine glands. The section on the liver is the best feature of the book, as it reviews well most of the complex features of liver metabolism: the formation of bile and bile salts, the significance of the direct and indirect Van den Bergh test, the formation of urea, glycogen storage, and metabolism, cholesterol formation and the relation of the liver to the serum proteins. The problem of renal function is also well covered, particularly with reference to chloride metabolism and renal and prerenal azotemia. In each section the functions which can be investigated, and those which cannot, are listed. The physiology of the organ is then discussed, followed by the laboratory methods that are available. Lastly, the results found in various pathologic states are tabulated, with suggestions as to what tests are of most value in the differential diagnosis of any given condition, as jaundice. While there is little that is new to the American reader in this volume, it is comprehensive in its survey of diagnostic methods. It should commend itself for use as a practical working guide in deciding which laboratory tests to use and the significance of the results obtained.

The Baby's First Two Years. By Richard M. Smith, A.B., M.D., Sc.D., Assistant Professor of Pediatrics and Child Hygiene, Harvard Medical School and School of Public Health, Boston. Fourth edition. Cloth. Price, $1.75. Pp. 121, with 20 illustrations. Boston: Houghton Mifflin Company, 1937.

This book, dealing with the growth and development of the baby from birth to the age of 2 years, has found a wide usage. The author has detailed equipment necessary for the comfort of the baby. There are descriptions of ideal surroundings for the home and nursery. The feeding, both breast and artificial, habits, training and care during sickness are described. Suggestions are given to the mother for the care of herself, and traveling with the baby is made easy through a description of the facilities necessary during travel. Appended are recipes for the preparation of infant foods. The illustrations which have been added in this edition are clear and excellent in detail.

Grundriss einer Meteorobiologie des Menschen: Wetter- und Jahreszeiteneinflüsse. Von Professor Dr. B. de Rudder, Direktor der Univ.-Kinderklinik Frankfurt a. M. Second edition. Paper. Price, 12.60 marks. Pp. 234, with 59 illustrations. Berlin: Julius Springer, 1938.

In this volume de Rudder presents a good review of past clinical studies on weather and seasonal relationships in the incidence of disease, largely restricted, however, to publications in the German language. This review and extensive bibliography of German articles will prove useful to workers in other lands to whom many of the original publications may not be available. About 450 German papers on weather and seasonal influences are listed and discussed, while reference is made to only about sixty in the English language, sixteen in French and three in Italian. In another sense also the work is quite a local product, for it deals largely with weather and seasonal effects as manifested in the storm belt of the middle temperate part of Europe. In this respect it is similar to much of the material presented in Petersen's volumes "The Patient and the Weather," which are largely limited to effects of weather in the stormy middle temperate regions of North America. Neither Petersen nor de Rudder deals with the broader aspects of the effects of weather as manifested also in nonstormy temperate regions or in subtropical and tropical warmth.

Studies and publications on weather and seasonal relationships with human health have in recent years become top-heavy along the lines of clinical observation and disease statistics. More fundamental studies under experimentally controlled conditions are badly needed if the complex effects of the various weather factors are to be analyzed and evaluated. More general observations under widely diverse natural climates and weather conditions must also be made. This volume by de Rudder makes no contributions along these more fundamental lines of meteorobiology. As a review of more of less localized clinical observations and correlations between weather and the occurrence of disease it fills a useful function, but the reader should bear in mind that here is presented an incomplete and one-sided picture of the general field of human meteorobiology. However, within the limited scope of his work de Rudder makes a clear and well systematized presentation.

There remains little doubt that short-cycle and seasonal changes in meteorologic states do quite definitely affect the

incidence of a great variety of human ailments. De Rudder leans heavily toward associating these human effects with the passage of polar and tropical "fronts," a view so ably upheld in America by Petersen in his many-volumed "The Patient and the Weather." The writings of both men are of great value in stressing the importance of the weather factor and in indicating the urgent necessity for an experimental analysis of the problem under controlled conditions.

Anniversary Volume: Scientific Contributions in Honor of Joseph Hersey Pratt on His Sixty-Fifth Birthday. By His Friends. Cloth. Price, $7. Pp. 983, with illustrations. Lancaster, Pa.: Lancaster Press, Inc., 1937.

The group of papers here assembled represents a tribute to Dr. Joseph H. Pratt from his friends and students. It constitutes a tribute in the German manner of the festschrift to one of the ablest and best known of American physicians. It was hoped to include articles from Professors Krehl of Heidelberg and Morawitz of Leipzig, but their deaths unfortunately prevented these contributions. The individual papers, many of which have been published in the *Annals of Internal Medicine,* cover a wide range of subjects in experimental and clinical medicine. Among them may be mentioned those on the cardiac neurosis by White and Glendy, Bacillus Friedländer infections by Baehr and his associates, vitamin C and infection by Faulkner and Taylor, adrenal cortical tumor by Lawrence, effect of vitamin C on culture of tubercle bacilli by Heise and Steenken, several on various phases of medical history, and three on gout. Certainly no physician could receive a finer tribute than has Pratt in this group of splendid articles.

Leukemia and Allied Disorders. By Claude E. Forkner, A.M., M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School, New York. Cloth. Price, $5. Pp. 333, with 79 illustrations. New York: Macmillan Company, 1938.

It is perhaps surprising that a useful monograph of this size can be written about a disease which is defined in the first sentence as "an invariably fatal systemic disease of unknown etiology . . ." In compiling it, however, about 5,000 references have been consulted by the author, and the more important of these (about 1,600) are cited in the text and given in full at the end of the book. A real need is thus fulfilled and for the first time the important knowledge of leukemia to date is gathered together in one place and accompanied by such an extensive bibliography that the important original references can be easily located and consulted. The organization of the book is logical and should appeal to the neophyte in blood disease as well as to the specialist. There are a few errors, among which may be noted the legend for plate 1. The type could be more legible, but this is a minor criticism. While in no sense a contribution for the casual reader, this book is invaluable for a student of blood diseases and for the person who may wish to initiate original work in this field.

Studies on the Physiology of the Middle Ear. By J. Grandson Byrne, M.A., M.D., LL.D. Cloth. Price, 18s. Pp. 298, with 54 illustrations. London: H. K. Lewis & Co., Ltd., 1938.

This work will appeal primarily to the physiologist interested in hearing and to otologists capable of investigative work on this special sense on animals in a properly set up laboratory. The author concerns himself in large part with studying movements of the membrana tympani under varying experimental conditions. The different movements are graphically recorded and the experiments are done mostly on cats and dogs. By means of the necessary controls, tracings of the motions of the membrana tympani are made after administration of various drugs such as epinephrine and pilocarpine and following interference with or stimulation of the nervous pathways, incoming and outgoing, to the middle ear. The clinical significance of the various experiments and phenomena evoked are discussed in a brief fashion and the results obtained are compared with similar neuromuscular mechanisms affecting the pupils, lens and eyelids. For the practicing otologist the book may not present great interest. It does, however, bring rather forcibly to mind the increased attention that is being manifested in the physiology of the entire mechanism of hearing in the past few years, which received such great impetus from the phenomena uncovered by the work of Wever and Bray and from the increasing use of the exact methods of audiometry. More and more it seems clear that additions to knowledge in this special field in the immediate future at any rate will not come from the practicing otologist as they have in the past but to the greatest extent from the laboratories of the psychologist, the physicist and the physiologist, often collaborating.

Applied Pharmacology. By A. J. Clark, M.C., M.D., F.R.C.P., Professor of Materia Medica and Pharmacology in the University of Edinburgh. Sixth edition. Cloth. Price, $5. Pp. 678, with 84 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1938.

Since 1923, when Clark's Applied Pharmacology first appeared, it has been a helpful introduction to rational drug therapy based on sound physiologic principles and on the application of demonstrable actions of chemicals on living tissues. The present edition brings the book strictly down to the present with extensive changes including discussions on such new drugs as cyclopropane, vinethene, evipal, mandelic acid, sulfanilamide, carbarsone and the sterol hormones. The introductory chapter gives a brief but good review of systems of medicine and the basis for the practical applications of pharmacology. The discussion of principles of drug action has been expanded. The important subject of biologic standardization of drugs is too briefly considered and deserves fuller treatment. Considerable rearrangement of material has been made, disinfectants and chemotherapy being placed at the end of the volume instead of at the beginning. There is an excellent consideration of autopharmacology and of the endocrine glands. Throughout the volume appropriate discussions of physiologic principles introduce the analysis of pharmacologic evidence in order to lead to sound applications in therapy. An admirable illustration of this type of treatment is afforded in the chapter on respiration. Clark's Applied Pharmacology is now a standard textbook. It is useful not only for medical students but for practicing physicians. Unfortunately in this edition references to monographic and periodical literature have been considerably reduced. References only to general literature are afforded and these are not very extensive. The volume should not be considered as a reference work but rather as a well organized textbook.

Dyke's Automobile and Gasoline Engine Encyclopedia: The Elementary Principles, Construction, Operation and Repair of Automobiles, Gasoline Engines and Automobile Electric Systems; Including Trucks, Tractors, Motorcoaches, Automotive Diesel Engines and Motorcycles; Simple, Thorough and Practical. By A. L. Dyke. Eighteenth edition. Cloth. Price, $6. Pp. 1,312, with illustrations. Chicago: Goodheart-Wilcox Company, Inc., 1937.

There are times when physicians may wish to know a bit more about the technical side of the automobile he is driving. He may wish to be more conversant with repair men in understanding their terminology. The eighteenth edition of Dyke's Automobile and Gasoline Engine Encyclopedia contains information on all of the leading makes of automobiles and on different types of gasoline engines as well as the principles of the construction, operation troubles, tests, adjustments and repairs of automobiles and their component parts. This volume has been on the market for more than twenty-seven years and has served as a reliable guide for mechanics and automobile owners. This edition also contains new subjects; for example, many of its readers may find the information on the Diesel engines of considerable interest. This type of engine appears to be gaining in importance, particularly for use in trucks, tractors and busses.

Fever Therapy: Abstracts and Discussions of Papers Presented at the First International Conference on Fever Therapy, College of Physicians and Surgeons, Columbia University, New York City, March 29, 30, 31, 1937. Cloth. Price, $5. Pp. 486. New York: Paul B. Hoeber, Inc., 1937.

This volume is a useful record of a congress which correlated international work in a rapidly advancing field of therapeutics and demonstrated American leadership in the new realm. However, only the concise abstracts of the papers are printed, in the three official languages of the conference, English, French and German; the English section, in addition, contains the discussions. Thus the student looking for the full contents of any paper must seek elsewhere. The abstracts of the forty-five papers are conveniently grouped under divisions on physiology and pathology, fever therapy of miscellaneous diseases, fever therapy in syphilis and fever therapy in gonococcic infections. The volume also contains messages from the White House and from the honorary presidents, Wagner-Jauregg of Vienna and the venerable d'Arsonval of Paris.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Optometry Practice Act: Revocation of License for Nonpayment of Annual Registration Fee; Necessity for Notice of Revocation Proceedings.—One section of the Wyoming optometry practice act (Revised Statutes 1931, section 79-109) authorizes the board of examiners in optometry to revoke the license of a licentiate guilty of stated acts, after the licentiate has been given written notice of the charges against him and afforded an opportunity to defend himself, but on the revocation of a license the holder may appeal to the appropriate district court. Another section (section 79-110) requires every optometrist to pay an annual registration fee of $2 before April 1 and provides that if a licentiate defaults in the payment of this fee his license may be revoked by the board "upon twenty days' notice of the time and place of considering such revocation," but this section makes no provision for an appeal to the courts from any judgment the board may render.

Frenzel, a licentiate of the Wyoming optometry board, moved from that state to Illinois in 1929. On January 12 of that year he tendered a check in payment of his annual registration fee for the year, but it was apparently not presented for payment until more than a month had elapsed and when presented it was not honored by the bank on which it was drawn, on account of insufficient funds. On April 24, 1929, the board addressed a registered letter to Frenzel at a stated address in Chicago, informing him that his license had been suspended and would probably be revoked at a stated meeting of the board to be held May 27, 1929. The letter was never received by Frenzel, as he had lived at the address stated for only a short time. On the date named the board revoked his license. Frenzel, however, at dates that are in dispute, made tenders of the statutory registration fees and requested that a license be issued to him. On the board's refusal so to do, he brought an action of mandamus to require the board to issue a certificate to him. The trial court rendered judgment in his favor and the board appealed to the Supreme Court of Wyoming.

The board contended first that, since the optometry practice act has provided that an appeal may be taken from the action of the board in revoking a license, mandamus was not the proper remedy. The Supreme Court pointed out, however, that the appeal authorized by section 79-109 of the act relates exclusively to the revocation proceedings authorized in that section, in instances in which licenses have been revoked for the causes there stated. It is apparent, said the court, that there is good reason for an appeal to the court in such a case, but no such reason exists in the case of a revocation of a license on account of the nonpayment of an annual registration fee. No evidence need be taken and the hearing on the question of revocation is but formal. Moreover, if notice is not received by the licentiate, he would have no opportunity to appeal. The provision in reference to an appeal to the courts, said the Supreme Court, cannot be held to apply in such a case and the contention that mandamus is not the proper remedy must be overruled.

The board next contended that it was the duty of the licentiate to pay the fee prescribed in the section requiring an annual registration fee and that the licentiate is charged with knowledge of that duty. That, said the court, is correct. At the same time, the board is one created by statute; its powers are limited to those prescribed by the legislature, and it must in the exercise of any power granted comply at least substantially with statutory provisions. The board contended, however, that it was not necessary to serve on the licentiate the notice required by law; that all that was necessary was that the board should make an honest attempt to serve notice; and that the notice was not ineffectual if, as in this case, it is sent to the last known post office address of the licentiate. But, said the court, the statute provides that twenty days' notice of the time and place of considering the revocation should be given. To provide for notice without service thereof would be futile; provision for notice necessarily includes the duty to serve it, and the Supreme Court has held that, where notice is required to be served, its service must be personal, unless otherwise provided by statute, but that in the absence of a statute to the contrary, service may be made through the United States post office. The service in this case, however, attempted through the post office, was unsuccessful, and accordingly no notice whatever was given. The argument that an attempt, in good faith, to give notice, is a sufficient compliance with the statute and takes the place of actual notice is not sound. There was a purpose in making the provision, to give a further opportunity to the licentiate to comply with the law. It may be that the legislature might have dispensed with notice altogether. But it has not done so. It is not improbable that, when the legislative act in question was passed, no thought was given to situations like that confronting us here. That can be remedied in the future. But in this case, the law must be applied as we find it. The attempted revocation of the license of Frenzel, said the Supreme Court, was ineffective, and the judgment of the trial court directing the board of examiners in optometry to issue him a license was affirmed.—*State ex rel. Frenzel v. Wyoming State Board of Examiners in Optometry (Wyo.), 74 P. (2d) 343.*

Privileged Communications: Disclosure of Condition by Patient as Waiver.—In a suit instituted by the plaintiff on a health and accident insurance policy, the defendant insurance company denied liability, alleging that the plaintiff in applying for insurance made certain false statements concerning his previous health and concealed facts pertinent to his then state of health. The policy was issued in June 1933 and, according to the plaintiff, he became disabled on July 14, 1934. At the trial the plaintiff testified in some detail concerning his then present physical condition. On his behalf a physician stated that the plaintiff became his patient on July 14, 1934, and testified fully as to his physical condition when he first examined him and on subsequent dates. The insurance company sought to show by another physician who had treated the plaintiff from 1931 to early in 1933 that the plaintiff had had pneumonia and was suffering at the date of the application of insurance from endocarditis, of which the plaintiff was fully aware. The trial court, however, held that such testimony was barred by the sections of the Nebraska statutes relating to privileged communications. From a judgment in favor of the plaintiff, the insurance company appealed to the Supreme Court of Nebraska.

One section of the Nebraska statutes (section 20-1206, Comp. St. 1929) provides that no practicing physician shall be allowed in giving testimony to disclose any confidential communication properly entrusted to him in his professional capacity and necessary and proper to enable him to discharge the functions of his office according to the usual course of practice. The following section (section 20-1207, *ibid.*), however, provides that the prohibition of the preceding section shall not apply to cases in which the patient in whose favor the provision operates waives the privilege thereby conferred and that if a patient, a party to any action, offers evidence with reference to his physical or mental condition or the alleged cause thereof the privilege conferred in the preceding section shall be deemed to have been waived as to any physician or surgeon who has attended that party. The plaintiff contended, however, that the waiver contemplated by the last section applied only to physicians who might have examined him after the disability in controversy began. Since the plaintiff and his physician fixed the beginning of disability as of July 14, 1934, and their testimony as to his physical condition was confined to that date and subsequent times, their testimony, plaintiff contended, did not operate as a waiver of privilege as to any physician who had examined him before that date.

The difficulty with that line of reasoning, said the Supreme Court of Nebraska, is that the law makes no such distinction, and courts are not inclined to read into a statute exceptions that the legislature has not seen fit to make. The purpose of the enactment making disclosures by a patient to his physician confidential was to encourage the patient more freely to disclose his ailments, because of the knowledge that such information could not be divulged to his humiliation or disgrace. Where the patient himself makes a disclosure of his condition, there can be no humiliation or disgrace in showing that such condition existed over a longer period of time than the patient in his dis-

closure may have indicated. Such was the purpose of the testimony proffered by the insurance company in this case and it was material to the issues and should have been received. The statute was never intended as a cloak for injustice or fraud and to give it the construction contended for by the plaintiff would in many instances lead to just that result. The Supreme Court accordingly held that it was error for the trial court to refuse the testimony of the physician produced by the insurance company and reversed the judgment of the trial court and remanded the cause for a new trial.—*Ansnes v. Loyal Protective Ins. Co. of Boston, Mass. (Neb.), 276 N. W. 397.*

Workmen's Compensation Acts: Compensability of Heat Stroke.—The claimant's husband was employed by the defendant company to deliver ice on a commercial route. On July 11, 12 and 13 the heat was extreme, the temperature reaching a maximum of 106 F. during the day. On the evening of July 11 he was more tired than usual after his day's work. On July 12, after delivering ice until noon, he quit for the rest of the day; he complained of the heat and staggered on walking. On July 13 he returned to work but a helper made most of the deliveries for him. Late that afternoon, on his way home from work, he was overcome by the heat and suffered what was described in the medical testimony as a "collapse." He died the following day and an autopsy confirmed the diagnosis of heat stroke as the cause of death. The claimant thereupon brought proceedings under the workmen's compensation act of Minnesota against the employer for compensation for the death of her husband. From an order of the industrial commission awarding compensation, the employer appealed to the Supreme Court of Minnesota.

The employer contended that the claimant's husband had not sustained an accident within the meaning of the workmen's compensation act because this particular heat stroke was "of slow, gradual onset." The Supreme Court, however, could not agree with that contention, citing Minnesota cases to show that in that state heat stroke is accidental per se. Following those decisions, the court held that the heat stroke in the present case was accidental. Furthermore, in the opinion of the court, the accident occurred in the course of the deceased's employment even though his collapse had not occurred during his working hours. It is enough, said the court, that the causative agency was applied during the employment and was followed directly and immediately by the collapse without the intervention of a cause independent and unrelated to the employment. Accordingly, the Supreme Court affirmed the order of the industrial commission awarding compensation.—*Ueltschi v. Certified Ice & Fuel Co. (Minn.), 276 N. W. 220.*

Workmen's Compensation Acts: Strain in Relation to Kinking of Ureters.—The claimant brought suit under the workmen's compensation act of Louisiana against his employer and his employer's insurance carrier to recover compensation for disability allegedly due to injuries to his back, kidneys and ureters as the result of his lifting a heavy iron pipe or his being jerked to the ground by the pipe. From a judgment awarding compensation to the claimant for permanent and total disability, the claimant's employer appealed to the court of appeal of Louisiana, second circuit.

The evidence presented at the trial tended to show that the claimant had sustained a strain of the lumbar region of his back or an injury to the muscles of his back. Urinalyses were of no pathologic significance. A medical witness for the claimant, a urologist, testified that cystoscopic and roentgen examinations of the claimant's kidneys and ureters revealed kinks of both ureters and a downward displacement of the left kidney with "enlargement of the functioning part of that kidney" but with no actual impairment of function. Two medical witnesses for the defendant, a roentgenologist and a urologist, testified that cystoscopic, urologic and roentgen examinations of the claimant's kidneys and ureters showed a slight hydronephrosis of the right kidney and kinks in both ureters. According to their testimony the left kidney was normal. They failed to find any evidence of any displacement of either kidney.

The medical testimony presented, said the court of appeal, was conflicting. Some of the medical witnesses were of the opinion that the claimant's condition was caused by the strain or jerk and that it was sufficient to render him totally and permanently disabled. Other medical witnesses, however, were equally positive that his condition was not traumatic but was congenital and that he was not disabled. Although from a numerical standpoint, said the court, the medical witnesses favored the claimant's theory, testimony must be considered in the light of probability and not by counting the number of witnesses on each side. In the present case the evidence showed that the pain of which the claimant complained was confined to the left side of his back and yet there was no hindrance to the natural drainage of the left kidney. Many people, remarked the court, possess kinks in their ureters which are just as severe as the ones the claimant had and yet they experience no ill effects therefrom and are able to perform manual labor. Accordingly, the court of appeal concluded that the claimant had failed to prove that he was entitled to compensation and so reversed the judgment of the trial court awarding compensation.—*Jones v. Hunsicker (La.), 177 So. 262.*

Miscarriage Resulting from Shock.—A watchman employee of the defendant oil company, suspecting that the plaintiff's husband was attempting to obtain a can of gasoline stolen from the property the watchman was guarding, shot at a car the husband was driving. The plaintiff, who was riding in the back seat, suffered a skin wound to the right of the occipital region. She was two months pregnant at the time and subsequently suffered a miscarriage. She sued the defendant oil company, alleging that the miscarriage was a result of the shock of being shot. She alleged further that she had suffered "a serious and permanent derangement of her female organs and functions as a result of the miscarriage and shock." At the trial her attending physician attributed the miscarriage to the shock of being shot. There was no medical testimony, however, to connect any derangement of her female organs and functions with the miscarriage or the shock. From a judgment for $25,000 in her favor, entered on the verdict of the jury, the defendant appealed to the Supreme Court of Oklahoma.

It is well settled, said the Supreme Court of Oklahoma, that where a person's physical condition is such that medical testimony is necessary to describe it and to state its cause, such medical testimony must be given to the jury before a trial court is justified in submitting the issue to it. There was competent evidence in this case on which to submit to the jury the issue as to whether the plaintiff was shot and whether the miscarriage resulted from the resulting shock. There was, however, no evidence that any other injury resulted from the shot. Consequently, the trial court was not justified in submitting to the jury the issue arising out of the alleged injury to the plaintiff's female organs and functions, and its submission was prejudicial. The wound from the shot was inconsequential. The miscarriage, of course, was a serious matter. But the emphasis laid on the plaintiff's condition with relation to her female organs and functions undoubtedly, the court thought, accounted for the large verdict in the case. The court regarded the verdict for $25,000 as excessive and accordingly reversed the judgment in favor of the plaintiff.—*Empire Oil & Refining Co. v. Fields (Okla.), 73 P. (2d) 164.*

Society Proceedings

COMING MEETINGS

Colorado State Medical Society, Estes Park, Sept. 7-10. Mr. Harvey T. Sethman, 537 Republic Bldg., Denver, Executive Secretary.
Idaho State Medical Association, Sun Valley, Sept. 6-10. Dr. Harold W. Stone, 105 North Eighth St., Boise, Secretary.
National Medical Association, Hampton, Va., Aug. 15-19. Dr. John T. Givens, 1108 Church St., Norfolk, Va., General Secretary.
Oregon State Medical Society, Timberline Lodge, Aug. 24-27. Dr. Morris L. Bridgeman, 1020 S.W. Taylor St., Portland, Secretary.
Society of American Bacteriologists, San Francisco, Aug. 30-Sept. 1. Dr. I. L. Baldwin, College of Agriculture, University of Wisconsin, Madison, Wis., Secretary.
Utah State Medical Association, Ogden, Sept. 1-3. Dr. D. G. Edmunds, 610 McIntyre Bldg., Salt Lake City, Secretary.
Washington State Medical Association, Bellingham, Aug. 29-31. Dr. V. W. Spickard, 1303 Fourth Ave., Seattle, Secretary.
Wyoming State Medical Society, Laramie, Aug. 7-9. Dr. M. C. Keith, 156 South Center St., Casper, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1928 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but may be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Pathology, Boston

14: 253-384 (May) 1938

Degenerative Arthritis: Comparison of Pathologic Changes in Man and Equines. G. R. Callender and R. A. Kelser, Ancon, Canal Zone.—p. 253.

Studies on Experimental Rickets in Rats: II. Healing Process in Head of Tibia and Other Bones. G. S. Dodds and Hazel C. Cameron, Morgantown, W. Va.—p. 273.

Pars Intermedia Basophil Adenoma of Hypophysis. A. T. Rasmussen and A. A. Nelson, Minneapolis.—p. 297.

Study of Submaxillary Gland Virus of the Guinea Pig. F. S. Markham, Chicago.—p. 311.

*Bone and Cartilage Lesions of Protracted Moderate Scurvy. A. W. Ham and H. C. Elliott, Toronto.—p. 323.

Tuberculosis in Allergic and Desensitized Guinea Pigs: Study of Histologic Changes. H. S. Willis and C. E. Woodruff, Northville, Mich.—p. 337.

*Fatty Infiltration of Liver and Development of Cirrhosis in Diabetes and Chronic Alcoholism. C. L. Connor, San Francisco.—p. 347.

Primary Reticulum Cell Sarcoma of Lymph Nodes of Cow with Widespread Metastases. J. S. Bengston, Chicago.—p. 365.

Experimental Infection in the Mouse Produced by Intratracheal Inoculation with Haemophilus Pertussis. W. L. Bradford, Rochester, N. Y.—p. 377.

Bone and Cartilage in Scurvy.—Ham and Elliott object to the terms "subclinical, subscorbutic, latent and chronic scurvy" to designate the conditions produced by deficiencies of vitamin C. They suggest that the condition produced by a great deficiency be termed severe scurvy and that those conditions produced by lesser deficiencies be termed moderate and mild scurvy. They studied the epiphysial lesions of scorbutic conditions on five groups of guinea pigs: controls, those receiving no vitamin C and three groups each of which was subjected to a different degree of deficiency. The long bones of the animals which grew under a handicap of deficiency were only slightly shorter than those of the controls but they were much lighter, dried specimens weighing only about three fourths of similarly treated control bones. The bones of the experimental animals were fragile, rough and discolored and they frequently exhibited fractures of the shaft near the epiphysial plate. Many of the articulating surfaces were somewhat flattened and not uncommonly invaginated for a short distance into the epiphyses. Articular cartilage presents an uncalcified zone toward the joint cavity and a calcified zone toward the layer of bone which underlies and supports it. This shell of cartilage and underlying bone is normally supported by a scaffolding of cancellous bone. The uncalcified cartilage, the calcified cartilage and the supporting bone were all affected by protracted moderate scurvy. The supporting bone was diminished in amount and in some places there was none to support the cartilage. In some animals the zone of calcified cartilage encroached on the uncalcified cartilage so that a greater percentage of the articular cartilage was of the calcified variety. The uncalcified cartilage, in many sections, appeared thinner than normal. These fundamental changes were often accompanied by secondary changes. The weakened shell of cartilage and bone was often found distorted and fractured. Broken fragments of articular cartilage were found in masses of fibrous connective tissue which originated from the capsule. Capillaries were sometimes seen making their way into the uncalcified cartilage and these almost reached the surface in many instances. In some places, in which the cartilage had given way, the surface was covered with a layer or several layers of large cells with eccentrically located nuclei and basophilic cytoplasm. These cells resembled osteoblasts but were not associated with the matrix of the bone. The tips of the menisci in knee joints were often fibrinous in character. The connective tissue capsule of the joint, as well as the muscles associated with the joint, also showed lesions.

Fatty Infiltration of Liver and Cirrhosis.—According to Connor, fatty infiltration of the liver occurs in those conditions in which, because of a deficient intake or absorption of food, fat is mobilized from the existing fat depots and in which because of internal interference with the metabolism of fat due to anoxemia or tissue anoxia the accumulated fat cannot be broken down for use. In the starvation accompanying progressive morbid states the condition is of little pathologic importance, being in most cases terminal in nature. In diabetes the enlarged fatty liver may be influenced by insulin and by strict dieting but also may persist for many years. In alcoholism a variety of factors operate to produce the same condition. Alcohol alone will cause some fatty infiltration, but, as relative and sometimes absolute starvation is constantly associated with severe chronic alcoholism, fatty infiltration of the liver most often depends on a combination of these two. A liver containing demonstrable neutral fat is in most cases pathologic. Perilobular fibrosis seems to be the result of a combination of mechanical pressure, local tissue anoxia and general anoxemia, causing atrophy and degeneration of the cells of the liver. There are two types of liver in addicts to alcohol, one of which is the precursor of the other. The first is the enlarged tense liver so swollen with fat that the distended surface lobules present the appearance of cirrhosis. This effect is further simulated by the intrahepatic block, which interferes with the excretion of bile and the transmission of portal blood. The clinical signs of jaundice and ascites are thus produced. At necropsy the large liver is the only prominent finding. The lobules are distended with fat and some show, in addition, hyaline degeneration and atrophy of the peripheral cells associated with early proliferation of the fibroblasts. In the second form further proliferation of the connective tissue produces the typical picture of portal cirrhosis as seen in chronic alcoholism. The absence of fat in many such livers is explained by the exhaustion of body fat, by discontinuing the consumption of alcohol and resuming a normal or a high carbohydrate diet.

American Journal of Psychiatry, New York

94: 1259-1510 (May) 1938

Paresis: Analysis of 511 Treated Cases. R. A. Matthews, Philadelphia; R. S. Bookhammer, Norristown, Pa., and W. H. Izlar, Miami, Fla.—p. 1259.

Adjustment and Its Limits. E. Kahn, New Haven, Conn.—p. 1277.

Clinicopathologic Considerations for Differential Diagnosis Between Juvenile Paresis and Other Forms of Encephalitis. A. Ferraro, S. E. Barrera, New York, and H. S. Gregory, Binghamton, N. Y.—p. 1291.

Abstract of "One Hundred Years of Nonrestraint." E. Messinger, Northport, N. Y., and M. K. Amdur, Augusta, Ga.—p. 1307.

Pharmacologic "Shock" Treatment of Chronic Schizophrenia. I. M. Rossman and W. B. Cline Jr., Wingdale, N. Y.—p. 1323.

Observations in Hypoglycemic Treatment of Fifty-Five Cases of Schizophrenia. D. Ruslander, Buffalo.—p. 1337.

Treatment of Psychoses with Pentamethylenetetrazol. H. H. Goldstein, E. F. Dombrowski, J. V. Edlin, A. P. Bay, C. L. McCorry and J. Weinberg, Chicago.—p. 1347.

*Blood Chemical Changes Occurring in Treatment of Psychogenic Mental Disorders by Metrazol Convulsions: Preliminary Report. S. Maurer, H. O. Wiles and C. M. Marberg, Chicago, B. Skorodin and M. L. Fisher, Manteno, Ill.—p. 1355.

Rabies Vaccine in Treatment of Epilepsy. I. Finkelman, A. J. Arieff and M. A. Schiller, Chicago.—p. 1363.

Use of Intravenous Methylene Blue in Status Convulsivus. L. Kajdi, Baltimore, and C. V. Taylor, Sykesville, Md.—p. 1369.

Statistical Contributions from the Mental Hygiene Study of the Eastern Health District of Baltimore: II. Psychosis in the Eastern Health District: 1. Incidence and Prevalence of Psychosis in the Eastern Health District in 1933. B. M. Cohen and Ruth E. Fairbank, Baltimore.—p. 1377.

Organic Background of Obsessions and Compulsions. P. Schilder, New York.—p. 1397.

Psychoanalytic Clarification of Personality Types. E. E. Hadley, Washington, D. C.—p. 1417.

Psychoanalytic Contributions to Conception of Disorder Types. N. L. Blitzsten, Chicago.—p. 1431.

The Psychology of the Swindler. W. Bromberg and S. Keiser, New York.—p. 1441.

Parotid Gland Secretions in Manic-Depressive Patients. E. I. Strongin and L. E. Hinsie, New York.—p. 1459.

Blood Chemistry and Metrazol Convulsions.—Maurer and his associates have thus far used metrazol in the treatment of fifty-eight patients with psychogenic mental disorders at the Manteno State Hospital. They made quantitative measure-

ments of the p_H, lactic acid, dextrose, carbon dioxide, phosphorus, calcium and chloride of the blood of nine patients before, during and at intervals after the convulsions produced by metrazol. The study showed (1) a marked acidosis during and immediately after the tonic convulsion, the blood acidity being as high as is compatible with life, (2) a profound shift in some of the electrolytes and (3) a recovery phase, varying in duration, in which the body recovers its chemical equilibrium. The chemical changes are sufficiently uniform in all patients for one to predict what levels may be expected during any phase of the convulsion.

Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

39: 673-848 (May) 1938

*Roentgenographic Studies of Excretion of Dusts from Lungs. A. E. Barclay, K. J. Franklin and R. G. Macbeth, Oxford, England.—p. 673.
Mediastinal Hernia in Absence of Pneumothorax. H. C. Maier, Ann Arbor, Mich.—p. 687.
The Meningiomas: From a Roentgenologic Point of View. C. W. Schwartz, New York.—p. 698.
Persistent Right-Sided Aortic Arch. L. H. Garland, San Francisco. —p. 713.
Developmental and Life Cycles of Thoracic Aortic Aneurysms. E. Freedman, C. S. Higley and H. Hauser, Cleveland.—p. 720.
Myelography with Thorotrast and Subsequent Removal by Forced Drainage: Experimental Study: Preliminary Report. W. A. Nosik and O. A. Mortensen, Madison, Wis.—p. 727.
Rupture of Congenital Solitary Kidney: Report of Case in Which the Diagnosis Was Made During Life. L. G. Ericksen, South Bend, Ind. —p. 731.
Calcinosis Universalis: Report of Case with Autopsy Findings. S. E. Gould, Eloise, Mich., and F. T. Raiford, Detroit.—p. 741.
*Leukopenia and Leukocytosis in Lymphoblastoma: Their Reaction to Roentgen Therapy. F. H. Decker, Peoria, Ill.; E. T. Leddy and A. U. Desjardins, Rochester, Minn.—p. 747.
Cervical Lymph Nodes in Intraoral Carcinoma: Surgery or Irradiation? J. J. Duffy, New York.—p. 767.
Irradiation of Cervical Glands in Carcinoma of the Mouth and Lip. H. W. Jacox, Pittsburgh.—p. 778.
Is Roentgen Irradiation of Value in Treatment of Pulmonary Metastasis from Mammary Cancer? N. Treves, New York.—p. 783.
Protracted Roentgen Therapy of Pharyngeal Lymphosarcoma. A. Jutras, Montreal.—p. 792.
Study of Back Scatter. Edith H. Quimby, L. D. Marinelli and J. H. Farrow, New York.—p. 799.
Methods of Applying Radium Element in Form of Needles and Tubes. G. C. Wilkins, Manchester, N. H.—p. 816.

Excretion of Dusts from Lungs.—Barclay and his collaborators have insufflated radiopaque dusts into the lungs of healthy cats, in order to study their manner and rate of elimination. The radiopaque dusts used were bismuth carbonate, powdered lead glass and bismuth subnitrate. When due precautions are taken, insufflations of these dusts do not cause damage to the lungs. Insufflated dusts are not carried farther into the lungs than the distal termination of the ciliated epithelium; i. e., the defense against the penetration of dry dusts into the alveoli is extraordinarily efficient. Insufflated bismuth carbonate, which is neutral or slightly alkaline in reaction, is usually excreted in from one to four days. The subnitrate, which is strongly acid in reaction, is excreted slightly more rapidly. Insufflated lead glass powder is usually excreted in from seven hours to two days. The acidity or alkalinity of substances introduced into the lungs had no pronounced effect on the rate of excretion. Dusts mixed with various fluids and introduced into the trachea were not arrested by the ciliated epithelium but passed into the alveoli, from which they were slowly excreted over periods of weeks. There was no roentgenologic evidence that the dusts in these fluids passed to the lymph nodes during their excretion, though particles as small as 0.15 mm. are detected in roentgenograms, if the contrast medium used is adequate. The technic is sufficient to give a standard by which one may gage the delay produced by pathologic processes occurring within the lungs. There is much to be said for the older technic of dust insufflation as opposed to that of injection of iodized oil.

Leukopenia and Leukocytosis in Lymphoblastoma.—Decker and his co-workers paid particular attention to the leukocyte count, before roentgen therapy was administered, of the 450 cases of lymphoblastoma observed at the Mayo Clinic. Leukocyte counts of 5,500 or less were considered as evidence of leukopenia, from 5,500 to 10,000 inclusive as normal and counts of more than 10,000 as evidence of leukocytosis. There were twenty-five cases of leukopenia, twenty cases in which the leukocyte count was normal and twenty cases of leukocytosis. The average differential leukocyte count, before treatment, of these three groups indicates the presence of a normal percentage of lymphocytes in the cases with initial leukopenia, with a diminishing percentage as the total leukocyte count increased to normal or above. On the other hand, the percentage of the polymorphonuclear leukocytes increases as the total leukocyte count rises, as is shown by a comparison of the average differential count, before treatment, of the three groups. Other than the lymphocytes and polymorphonuclear neutrophils there is little variation, unless the presence of 5 per cent transitionals is considered of some importance. As the total number of leukocytes increases, the percentage of polymorphonuclear neutrophils frequently increases, while the percentage of lymphocytes decreases proportionately, regardless of the duration of the disease. Eosinophilia was present in the group with initial leukopenia in a percentage greater than 5 in five cases. The highest percentage of transitional cells was 9; in several cases it was 6 per cent. Among the patients with initially normal counts, the highest percentage of transitional cells was 8.5. In the group with initial leukocytosis, the only variation of significance was the presence in one case of 42 per cent of eosinophilic cells; in all the other cases it was 5 per cent or less. After irradiation, the total leukocyte count fluctuated considerably. The leukocyte count of fourteen patients with initial leukopenia averaged 4,700 on their first visit, before any treatment had been given. Approximately four weeks later, after one roentgen treatment, the average leukocyte count was 3,957. The available data for the third visit were averaged; the leukocyte count was 4,270. The data beyond the third visit are extremely varied and do not permit generalization. The group with initially normal counts was analyzed in the same manner. The leukocyte count averaged 22.4 per cent less than before treatment and 33⅓ per cent less at the third visit. A study of the changes in the patients with initial leukocytosis shows that the average before treatment, 16,070 cells, was reduced to 6,866 cells, or 58.6 per cent less at the second visit, and had recovered only to a slight extent at the time of the third visit, when the average count was 7,900 even though partial or complete treatment was given in each instance. A comparison of the average differential counts in the group with leukocytosis, before the first treatment and four weeks after the first treatment, shows that the most marked destruction involved the polymorphonuclear leukocytes, both in percentage and in absolute numbers. From this study, leukopenia does not have any prognostic significance. Leukopenia in lymphoblastoma is not a contraindication to roentgen therapy. Initially normal leukocyte counts (between 5,500 and 10,000) occurred in 58.5 per cent of the series of 450 cases; a count of more than 10,000 in 36 per cent.

Annals of Internal Medicine, Lancaster, Pa.

11: 1925-2078 (May) 1938

The Function of the College. J. H. Means, Boston.—p. 1925.
New Experimental Data on Artificial Hyperthermia. A. Bessemans, Ghent, Belgium.—p. 1933.
Drugs in the Treatment of Heart Disease. R. L. Levy, New York.—p. 1946.
*Use of Mercurial Suppository as Diuretic. J. Flexner, New York.—p. 1962.
Some Public Health Aspects of Undulant Fever. H. G. Newman, St. Louis.—p. 1973.
Protamine Zinc Insulin in Diabetes. E. P. McCullagh, Cleveland.—p. 1979.
*Association of Sciatic Neuritis with Liver Disease. S. S. Lichtman, New York.—p. 1992.
*Response to Feeding of Cevitamic Acid in Normal and Deficient Subjects as Measured by Vitamin C Excretory Test. Elaine P. Ralli and G. J. Friedman, New York.—p. 1996.
Peptic Ulcer: Effect of Administration of Bile on Behavior of the Disease. E. S. Emery Jr. and M. A. Schnitker, Boston.—p. 2007.
Exercise Tests and the Electrocardiograph in the Study of Angina Pectoris. M. E. Missal, Rochester, N. Y.—p. 2018.

Mercurial Suppositories and Diuresis.—Flexner used mercurial suppositories on twenty occasions in ten patients with varying degrees of cardiac decompensation. These patients were treated regularly by rest in bed, sedation, digitalis and restricted fluid intake. In seventeen instances a

diuresis ranging from 1,950 to 8,750 cc. resulted in twenty-four hours from the use of the suppositories. In one of the failures the diuresis was delayed until the third day of ammonium chloride therapy. The other two failures were obtained in a case presenting renal complications. Renal insufficiency followed the mercurial suppositories and administration of ammonium chloride; the subsequent death of this patient was apparently caused by a cerebral embolus. In two cases of hepatic cirrhosis studied, mercurin suppositories did not seem to be the best form of administering mercury, as it produced rectal discomfort and there was no consistent increase in urinary output.

Sciatic Neuritis and Hepatic Disease.—Lichtman reports five cases which indicate that the symptoms of sciatic neuritis in some instances may be the precursors of hepatic insufficiency. Though an analgesic effect of hepatitis and jaundice on sciatic pain has been observed, the possible relationship between the jaundice and the antecedent sciatic pain has escaped notice. Such a relationship may be important, for the development of jaundice, sometimes fatal, has recently been ascribed to the use of cinchophen prescribed for its analgesic effect. Sciatic neuritis may be an early manifestation of a disease process which may lead to hepatic disease and insufficiency. Endogenous or exogenous toxic agents may affect peripheral nerves before their hepatic effects become manifest clinically. Careful interrogation with regard to the history has eliminated the possibility of cinchophen in any form in three of the cases cited.

Response to Ascorbic Acid.—Ralli and Friedman determined the three hour urinary excretion of vitamin C before and after an intravenous test dose of 100 mg. of ascorbic acid in twelve normal adults, three normal individuals on diets low in vitamin C and twenty-two cases of scurvy. The three and twenty-one hour excretion was studied in the same group after an intravenous test dose of 100 mg. of ascorbic acid and the intravenous test dose was repeated in all three groups following the feeding of ascorbic acid. Following the intravenous test dose the twelve normal subjects excreted an average of more than 40 per cent of the injected vitamin within three hours. The extremes were from 24 to 82 mg. The three patients with subnutrition excreted from 5 to 14 mg. The patients with scurvy excreted from 0 to 5 mg. Following the ingestion of 1,000 mg. of ascorbic acid to the subnutrition subjects, the three hour excretion rose to the normal level after the test dose. In order to increase the urinary excretion to the normal level in the patients with scurvy, much larger amounts of the vitamin had to be fed. In the normal group the ingestion of ascorbic acid in small doses increased the vitamin C excretion above the original level. Excretion tests were also done following an intravenous test dose of 500 mg. of ascorbic acid in normal and scorbutic subjects. The normal subjects excreted an average of 55.8 per cent and the scorbutic patients an average of 7 per cent. The results suggest that the urinary excretion of vitamin C following an intravenous test dose of 100 mg. of ascorbic acid will serve as an index of vitamin C deficiency or subnutrition and as a guide to show the degree of saturation of the tissues following the ingestion of ascorbic acid.

Archives of Otolaryngology, Chicago

27: 519-660 (May) 1938

Sulfanilamide in Treatment of Experimental Streptococcic and Pneumococcic Meningitis. J. A. Kolmer, with assistance of Anna M. Rule and Mary L. Werner, Philadelphia.—p. 519.

Studies in Mechanism of Action of Sulfanilamide: II. Sulfanilamide in Treatment of Experimental Streptococcic Meningitis. P. E. Adolph and J. S. Lockwood, Philadelphia.—p. 535.

Retropharyngeal and Cervical Emphysema: Report of Case. S. H. Gidoll, San Francisco.—p. 552.

Endaural, Antauricular Surgical Approach to the Temporal Bone: Principles Involved in This New Approach: Summary Report of 1,780 Cases. J. Lempert, New York.—p. 555.

Air Cells of Petrous Portion of Temporal Bone in a Child Four and a Half Years Old: Study Based on Wax Plate Reconstructions. B. J. Anson, J. G. Wilson and J. P. Gaardsmoe, Chicago.—p. 588.

Treatment of Chronic Catarrhal Deafness with the Eustachian Heat Bougie. E. Simon, Albany, N. Y.—p. 606.

Plastic Surgery, 1936-1938. R. H. Ivy and H. A. Miller, Philadelphia. —p. 622.

Archives of Pathology, Chicago

25: 777-940 (June) 1938

Inflammation of Serous Surfaces: Hydrogen Ion Concentration in Relation to Cell Type. B. Steinberg and A. Dietz, Toledo, Ohio.—p. 777.

Id.: Transfer of Living Leukocytes and Effect on Acute Infectious States. B. Steinberg, Toledo, Ohio.—p. 785.

Id.: Factors Modifying Types of Cell Response. B. Steinberg and Ruth A. Martin, Toledo, Ohio.—p. 792.

Loss of Acidophilic Granules from Pituitary of Guinea Pig Under Experimental Conditions of Increased Metabolism. Isolde T. Zeckwer, Philadelphia.—p. 802.

Bronchiogenic Distribution of Fluid and Particulate Matter: Its Site of Predilection and Mechanism of Transfer. H. S. Reichle, Cleveland. —p. 811.

Congenital Aneurysm of Membranous Septum. M. Lev and O. Saphir, Chicago.—p. 819.

*Lymphadenoid Goiter. C. A. Hellwig, Wichita, Kan.—p. 838.

"Aniline Tumors" of the Bladder. W. C. Hueper, Wilmington, Del. —p. 856.

Lymphadenoid Goiter.—Hellwig observed at St. Francis Hospital four cases corresponding in every detail with those reported by Hashimoto (struma lymphomatosa) and Williamson and Pearse (lymphadenoid goiter). His observations led to conclusions which are at variance with the view expressed by most writers. The cases suggest (1) that lymphadenoid goiter is a distinct pathologic and clinical entity and has no relation to Riedel's struma, (2) that it is not a true inflammatory process—not any more than so-called chronic cystic mastitis and (3) that the histologic changes characteristic of lymphadenoid goiter may be present in typical exophthalmic goiters. Lymphadenoid goiter is the result of a functional disorder. The cycle of colloid storage and release is fundamentally disturbed, and the exhaustion of colloid explains the symptoms of hypothyroidism, associated so often with this type of goiter. The underlying cause of lymphadenoid goiter is probably an excess of thyrotropic hormone.

Canadian Public Health Journal, Toronto

29: 203-254 (May) 1938

Some Fundamentals in Tuberculosis Prevention. R. G. Ferguson, Fort San, Sask.—p. 203.

Survey of Incidence of Venereal Diseases in Ottawa, Canada, November 1937. J. T. Clarke, Ottawa, Ont.—p. 213.

Notes on Early History and Evolution of the Department of Health of Montreal. E. Gagnon, Montreal.—p. 216.

Experimental Infection with Haemophilus Pertussis and Protection Tests in Mice. N. Silverthorne, Toronto.—p. 233.

*Brucellosis In and Around Vancouver. C. E. Dolman and Vivienne G. Hudson, Vancouver, B. C.—p. 236.

Brucellosis In and Around Vancouver.—From March 1936 to March 1938 Dolman and Hudson received and examined for Brucella agglutinins a total of 1,296 separate samples of raw milk from fifty-five dairies in Vancouver. Of this total, 704 samples (54.3 per cent) showed complete agglutination in one or more tubes of the range adopted, while a further 168 (13 per cent) gave a doubtful reading. Thus less than 33 per cent of the samples were completely negative for Brucella agglutinins. There were nine dairies among 213 samples of which no negative specimen was found. Three dairies which yielded no positive specimens among sixty samples and forty-three dairies and their 1,023 specimens of milk showed a great preponderance of positive and doubtful results. Samples of blood serum sent to the Provincial Laboratories for Widal tests during the last six years from some 5,420 persons have been tested regularly for Brucella agglutinins. The results obtained with one group of 5,068 specimens, sent in by physicians of Vancouver and adjacent municipalities, shows the incidence of positive samples to be 4.5 per cent. Few of these specimens were sent in under a provisional diagnosis of brucellosis, and there is no information regarding the clinical signs and symptoms from which the majority of the 228 persons with positive serums may have been suffering. The results shown by this group may be contrasted with those given by a group of 352 specimens received from employees of a logging camp and from residents of a paper pulp company town, living remote from Vancouver and its milk supply. In this group only two specimens, or 0.57 per cent, were positive and gave complete agglutination in serum dilutions no higher than 1:40 and 1:80 respectively. No attempt was made to trace the clinical history of every patient with a positive serum in these groups, but in

recent months, with the cooperation of the physicians concerned, fifteen cases of undoubted acute brucellosis have been diagnosed on both laboratory and clinical grounds. In every case the evidence has pointed to the consumption of raw milk as the primary etiologic factor.

Johns Hopkins Hospital Bulletin, Baltimore

62: 475-564 (May) 1938

Coarctation of Aorta with Unequal Blood Pressure in the Arms: Case Report. R. G. Hills, Baltimore.—p. 475.

*Cevitamic Acid Content of Fetal Blood. C. P. Manahan and N. J. Eastman, Baltimore.—p. 478.

Studies Concerning Hypertension in Childhood: I. Development of Essential Hypertension Under Observation. Helen B. Taussig and M. S. Hecht, Baltimore.—p. 482.

Id.: II. Occurrence of Hypertension in Acute Rheumatic Fever in Childhood. Helen B. Taussig and M. S. Hecht, Baltimore.—p. 491.

Researches on Tetanus: VII. (1) Time Required for Fixation of Fatal Quantity of Tetanus Toxin; (2) Return Passage of Toxin by Way of Lymphatic Capillaries to Cardiovascular System; (3) Return Passage as Basis of Method for Approximate Determination of Volume of Lymph in Closed Lymphatic System. J. J. Abel, Bettylee Hampil, A. F. Jonas and W. Chalian, Baltimore.—p. 522.

Ascorbic Acid in Fetal Blood.—Manahan and Eastman subjected twenty-five white women and the same number of Negresses, all taken at random, to venipuncture at the moment of delivery. Samples of fetal blood were also obtained by venipuncture of the umbilical vein. The two samples were analyzed for ascorbic acid by the method of Tillmans, Hirsch and Hirsch. To ten additional patients 100 cc. of orange juice was administered three times daily during the last few weeks of the antepartum period and the two bloods were analyzed at delivery for ascorbic acid. The results confirm those of Braestrup and leave little doubt that the content of ascorbic acid of the fetal blood is regularly from two to four times that of the maternal blood. The question arises whether the reducing substance which one analyzes in fetal blood as ascorbic acid is the true vitamin or is, partly at least, some other substance capable of reducing the phenolindophenol of the Tillmans procedure. The fact that it is possible to raise the concentration of ascorbic acid of the fetal blood by administering orange juice to the mother speaks against such a hypothesis. The relatively high concentration of ascorbic acid in the fetal blood suggests that the placenta exerts a selective action with respect to this vitamin.

Journal of Bacteriology, Baltimore

35: 455-560 (May) 1938

Studies on Anaerobiosis: I. Nature of Inhibition of Growth of Cyanide-Treated Escherichia Coli by Reversible Oxidation-Reduction Systems. R. H. Broh-Kahn and I. A. Mirsky, Cincinnati.—p. 455.

Method for Concentration of Poliomyelitis Virus in Nasopharyngeal Washings. J. R. Paul, with technical assistance of G. Blezinger, New Haven, Conn.—p. 493.

Dissociation of Single Cell Cultures of Staphylococcus Aureus. Rachel E. Hoffstadt and G. P. Youmans, Seattle.—p. 511.

Influence of Diet on Lactobacillus Acidophilus Content and Hydrogen Ion Concentration of Intestine. L. Weinstein, J. E. Weiss and R. W. H. Gillespie, New Haven, Conn.—p. 515.

Metabolism of Pathogenic Bacteria: I. Bacteriologic and Chemical Methods. T. E. Friedemann, Chicago.—p. 527.

Factors Influencing Rate of Fermentation of Streptococcus Lactis. O. Rahn, C. P. Hegarty and R. E. Deuel, Ithaca, N. Y.—p. 547.

Journal of Nutrition, Philadelphia

15: 411-524 (May) 1938

Effect of Varied Vitamin B Ingestion on Appetite of Children. F. W. Schlutz and Elizabeth M. Knott, Chicago, with cooperation of Nerinne Isaacson Stage and M. L. Reymert.—p. 411.

Studies on Vitamin B_1 Requirements of Growing Rats. A. Arnold and C. A. Elvehjem, Madison, Wis.—p. 429.

Relation of "Grass Juice Factor" to Guinea Pig Nutrition. G. O. Kohler, C. A. Elvehjem and E. B. Hart, Madison, Wis.—p. 445.

Technic of Measuring Radiation and Convection. J. D. Hardy and E. F. Du Bois, with technical assistance of G. F. Soderstrom, New York.—p. 461.

Basal Metabolism, Radiation, Convection and Vaporization at Temperatures of 22 to 35 C. J. D. Hardy and E. F. Du Bois, with technical assistance of G. F. Soderstrom, New York.—p. 477.

Effect of Urea on Human Respiratory Exchange and Alveolar Carbon Dioxide. T. M. Carpenter, Boston.—p. 499.

Basal Metabolism in Pregnancy. J. A. Johnston, Helen A. Hunscher, Frances Cope Hummel, Mary F. Bates, Priscilla Bonner and Icie G. Macy, Detroit.—p. 513.

Journal of Pediatrics, St. Louis

12: 563-700 (May) 1938

Focal Infection and Metabolism: Effect of Removal of Tonsils and Adenoids on Nitrogen Balance and Basal Metabolism. J. A. Johnston and J. W. Maroney, Detroit.—p. 563.

Immunologic Reactions for Undulant Fever in Apparently Healthy and in Tuberculous Children. J. R. Lewin and I. Gersh, Denver.—p. 571.

*Effects of Tannic Acid Nasal Sprays on Incidence of Upper Respiratory Infections. Margaret Harper McKee, Irvington, N. Y.—p. 576.

Hurler's Syndrome (Gargoylism): Summary of Literature and Report of Case with Autopsy Findings. R. J. Kressler and E. E. Aegerter, Philadelphia.—p. 579.

Ehlers-Danlos Syndrome. A. C. Rambar, Chicago.—p. 592.

Significance of Shigella Alkalescens (Andrewes): Clinical Appraisal of Nine Cases from Which Organism Was Isolated. P. V. Woolley Jr. and Marian Sweet, Boston.—p. 596.

*Care of Skin of the Newborn Infant—Prevention of Infection. L. H. Smith, Portland, Ore.—p. 603.

Granulocytopenia and Hyperleukocytosis Following Sulfanilamide Therapy. G. R. Alpert and R. P. Forbes, Denver.—p. 605.

*Use of Sulfanilamide in Gonococcic Infections in Children. J. W. Holmes, J. A. Jones and N. Gildersleeve, Philadelphia.—p. 610.

Simultaneous, Bilateral, Postdiphtheritic, Diaphragmatic Paralysis Treated by Mechanical Respirator, with Recovery. A. H. Neffson and S. M. Wishik, New York.—p. 616.

Active Immunization Against Pertussis with Formalized Vaccine. M. L. Blatt, I. M. Levin and I. E. Schapiro, Chicago.—p. 619.

Von Gierke's Glycogen Storage Disease: Case Report with Unusual Findings. M. M. Fliess, Clifton Forge, Va., and S. M. Bloom, New York.—p. 635.

Varicella Complicated with Acute Thrombocytopenic Purpura and Gangrene. A. V. Stoesser and W. W. Lockwood, Minneapolis.—p. 641.

Influence of Factors Before and at Time of Delivery on Premature Mortality. B. B. Breese Jr., Rochester, N. Y.—p. 648.

Tannic Acid Nasal Sprays and Catarrh.—In an effort to determine the effect of blocking the nasal passages on the incidence of the common cold McKee used a 4 per cent solution of tannic acid as a nasal spray. The 105 children with rheumatic disease used for the study were divided into two groups. The nasal passages of fifty-four were sprayed and fifty-one received no treatment and constituted the controls. Approximately 70 per cent of the children in each group had one or more infections of the upper part of the respiratory tract during the period of observation, November 1936 to April 1937, averaging 1.1 or 1.2 episodes per patient. In about 50 per cent of the cases the predominating symptoms and signs were localized in the throat and in the rest the nasal passages were mainly involved. The number of children having obvious chronic sinusitis, pharyngitis, coryza, adenitis and streptococcic infections was about evenly divided. Four untreated and only one treated child had frank tonsillitis associated with a marked elevation of temperature. The number of attacks of rheumatic fever in the two groups was nearly alike: three attacks in the treated and eight in the untreated children were preceded by infections of the upper part of the respiratory tract; of these, two in the treated and five in the control group were associated with streptococci. It is probable that blocking of the nasal passages affords effective protection only in those diseases which are caused by strictly neurotropic viruses.

Prevention of Cutaneous Infection of the Newborn.—According to Smith, since February 1935 oiling and bathing the newborn infant has been discontinued at the Multnomah County Hospital. Previous to this, a 1 per cent copper oleate had been used and a great reduction in the incidence of pyodermia ensued. But with 1,734 babies receiving no treatment only two cases of suggestive pyodermia occurred. The technic is simply not to clean the baby after birth; that is, the vernix caseosa is not removed. Excess blood is wiped off, but that is all. The skin is neither bathed nor oiled during the infant's stay in the hospital. Warm water is used to clean the buttocks following each stool. Each day the clothing is changed, but the infant is not bathed or oiled. Within twelve hours after birth the infant's skin is clean; the vernix has disappeared. The only areas to be watched are the axillae and the groin, for, if the vernix caseosa has not "dried" in these areas, the skin may remain moist and show irritation. It is believed that the lessened handling of the infant's skin prevents cutaneous infection. The most satisfactory treatment when any cutaneous irritation of the newborn occurs, even when pyodermia is suspected, is a powder composed of three parts of mercurous chloride, two parts of talcum and one part of zinc oxide.

Sulfanilamide in Gonococcic Infections in Children.—Holmes and his associates used sulfanilamide in fifty-one cases of gonorrhea in children. These included forty-seven cases of vulvovaginitis and four cases of urethritis in the male. Five of the girls were treated by means of suppositories containing sulfanilamide, the balance received the drug by mouth. Daily administration of 0.6 Gm. of sulfanilamide per 20 pounds of body weight gave practically no untoward effects. Three of the male patients failed to show any improvement. The five patients with vulvovaginitis treated by suppositories containing sulfanilamide showed no improvement. Of the forty-two patients with vulvovaginitis treated by sulfanilamide by mouth, only sixteen were temporarily relieved, and of these eight had recurrences.

Medical Annals of District of Columbia, Washington

7: 137-170 (May) 1938

The Mental Hospital of Yesterday and Today. W. Overholser, Washington.—p. 137.
*Wheat Germ Oil (Vitamin E) in Treatment of Repeated Spontaneous and Threatened Abortion: Preliminary Report. J. K. Cromer, Washington.—p. 145.
The Eye in Diabetes Mellitus. B. Rones, Washington.—p. 149.
Present-Day Treatment of Tuberculosis in Sanatoriums of the District of Columbia. J. W. Peabody, Washington, and D. L. Finucane, Glenn Dale, Md.—p. 153.
Endobronchial Tumors: Diagnosis and Treatment. E. W. Davis, Washington.—p. 157.

Wheat Germ Oil in Abortion.—Cromer gave wheat germ oil (vitamin E) to four women who had sustained one or more recurrent abortions prior to the vitamin E therapy. One of these went to term and delivered a full term, healthy child of 6 pounds 14 ounces (3,300 Gm.). One had a partial separation of the placenta at eight months and delivered an infant which weighed 4 pounds 9 ounces (2,190 Gm.). This infant survived. Another one terminated spontaneously about the twentieth week, eight weeks after wheat germ oil therapy was begun. The fourth patient went to term and delivered a normal female infant which weighed 7 pounds 4 ounces (3,480 Gm.). Three patients were treated for threatened abortion after the symptoms had begun. Of these, one went to term and delivered a normal child weighing 7 pounds 5 ounces (3,510 Gm.) without further trouble. Another had several episodes with cramps and bleeding but finally delivered a living child weighing 6 pounds 12 ounces (3,240 Gm.) two weeks before term after premature rupture of the membranes. The third patient, after several attacks of uterine pain with bleeding, finally went to term and delivered a normal female infant which weighed 6 pounds 6 ounces (3,060 Gm.).

Military Surgeon, Washington, D. C.

82: 385-484 (May) 1938

Veterans' Administration and Its Fight Against Tuberculosis: The Hospitalization of Tuberculous Veterans. F. T. Hines.—p. 385.
"The Doctor Stays at Home." C. L. Beaven.—p. 391.
Rabies in Coyotes. G. E. Ledfors and W. E. Seiler.—p. 400.
Umbilical Hernia: Case Report. F. J. Vokoun.—p. 416.
Report on Ninth International Congress of Military Medicine and Pharmacy: Comparative Study of Supply of Foodstuffs and Alimentation of the Sick and Wounded in Times of Peace and War. W. S. Bainbridge.—p. 417.
The Organization and Functions of the Medical Services in Combined Operations of Land and Sea Forces. W. L. Mann and E. E. Hume.—p. 439.
Simultaneous Bilateral Spontaneous Pneumothorax: Case Reports. L. J. Weinstein.—p. 453.
The Life of Charles Stuart Tripler. J. M. Phalen.—p. 459.

New York State Journal of Medicine, New York

38: 677-756 (May 1) 1938

Some Unusual Complications Associated with Abruptio Placentae. E. C. Hughes and A. W. Van Ness, Syracuse.—p. 677.
Tuberculin Test of School Children: Comparative Values. G. W. Weber, Albany; F. W. Holcomb, Kingston, and K. M. Murphy.—p. 685.
Carcinoma of the Skin: Practical Phases. J. J. Eller, New York.—p. 689.
The Complement Fixation Test: Diagnostic Aid in Control of Gonorrhea. Emily Dunning Barringer, New York.—p. 699.
Problem of Peripheral Vascular Disease. A. N. Curtiss, Syracuse.—p. 705.
Inhalation and Pneumatic Treatments. M. Weiss, New York.—p. 713.

Public Health Reports, Washington, D. C.

53: 701-746 (May 6) 1938

Trends in Shellfish Sanitation. H. N. Old.—p. 720.
Planning the Organization and Conduct of Stream Pollution Surveys. J. K. Hoskins.—p. 729.

53: 747-792 (May 13) 1938

Studies on Dental Caries: I. Dental Status and Dental Needs of Elementary School Children. H. Klein, C. E. Palmer and J. W. Knutson.—p. 751.
Experimental Vanadium Poisoning in the White Rat. Esther Peterson Daniel and R. D. Lillie.—p. 765.
Influence of Nonbreeding and Foster Nursing on Occurrence of Spontaneous Breast Tumors in Strain C_3H Mice. H. B. Andervont and W. J. McEleney.—p. 777.

Southern Medical Journal, Birmingham, Ala.

31: 579-708 (June) 1938. Partial Index

Pseudomycosis: Indolent Leg Ulcer: Study of Fifty-Four Patients. J. F. Hamilton, Memphis, Tenn.—p. 579.
*Arthus Phenomenon from Mosquito Bites: Report of Case with Experimental Studies. A. Brown, T. H. D. Griffitts, S. Erwin and L. Y. Dyrenforth, Jacksonville, Fla.—p. 590.
Heredity in Cancer of the Breast. M. J. Tendler, Memphis, Tenn.—p. 602.
Rupture of Biceps Brachii: Report of Fourteen Cases. R. L. Waugh, New Orleans.—p. 619.
Congenital Lung Cysts, Air Expansile Types. W. W. Anderson, Atlanta, Ga.—p. 628.
Urinary Findings in the Newborn: Report of Three Cases of Neonatal Nephritis. C. E. Conrad, Harrisonburg, Va.—p. 636.
Roentgenologic Treatment of Various Blood Dyscrasias. J. J. Clark, Atlanta, Ga.—p. 641.
Fatality from Acute Hemolytic Anemia Which Developed During Administration of Sulfanilamide. H. Wood, Charleston, S. C.—p. 646.
Circulatory versus Respiratory Deaths from Pentothal Sodium. C. Reynolds and J. R. Veal, New Orleans.—p. 650.
Analysis of 400 Instances of Chronic Bromide Intoxication. F. M. Hanes and Anne Yates, Durham, N. C.—p. 667.
Gastric Acidity as Manifestation of Extragastric Disease. F. L. Apperly, Richmond, Va.—p. 671.
Ethyl Esters of Chaulmoogra Oil Therapy in Treatment of Mycosis Fungoides. S. J. Wilson, Fort Worth, Texas.—p. 675.
Mycotic Infections in Otolaryngology. W. D. Gill, San Antonio, Texas.—p. 678.

Arthus Phenomenon from Mosquito Bites.—Brown and his collaborators report an instance of the phenomenon of Arthus, the causative agent of which was Aedes aegypti, a household mosquito common in the Southern states. Necrosis of the skin in this girl of 18 (at the time of death) resulting from mosquito bites is apparently unique in the literature. The formation of blebs, varying in size from a pea to a half dollar (30 mm.) but without subsequent necrosis and scarring, was first noticed when she was 2½ years old. In 1930, at the age of 11, the swelling of the arms and legs from multiple mosquito bites had persisted well into the fall and was accompanied by a hardness of the tissues, formerly absent. Thereafter the seasonal swelling coincident with the mosquito season had lasted longer each season, and the induration had become more marked and persistent after the disappearance of mosquitoes. In the opinion of Pusey, who saw the patient, this case was unlike any he had seen and he accepted the diagnosis of the Arthus phenomenon from the bite of Aedes aegypti. There was repeated and invariable demonstration of lesions occurring after experimental bites and progressing through characteristic and protracted evolution to typical scarring. The patient had a history of familial allergy. The type of lesion, its evolution and improvement in general health were unaltered by autogenous staphylococcus vaccine, mosquito vaccine, gonadotropic substance, thyroid medication and diet. The early characteristics of this case from the onset to the seventh year, when the lesions were bullous and healed without scar formation, were similar to the reactions described by Genner and Bode, suggesting that it was a more aggravated manifestation of a similar phenomenon due to the bite of an insect, in this instance Aedes aegypti. The positive Prausnitz-Küstner reaction would definitely place this case in the allergic category. Biopsies of delayed reactions, when necrosis was in progress, showed eosinophilic infiltration indicative of allergy. The blood eosinophilia of allergy was present five minutes after the patient was bitten by mosquitoes. Partial protection from bites by the intradermal injection of a normal person's blood serum into the patient, the reverse Prausnitz-Küstner reaction, constituted a measure of local passive immunity.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Anaesthesia, Manchester

15: 85-132 (April) 1938

"Death on the Table." G. Edwards.—p. 87.
Nembutal-Chloral Narcosis in Childbirth. F. B. Mallinson.—p. 104.

British Journal of Radiology, London

11: 273-344 (May) 1938

Radiologic Experience in Ventriculography. E. Lysholm.—p. 273.
Low-Voltage, Near-Distance X-Ray Therapy. J. F. Bromley.—p. 289.
The After-Care of Patients Suffering from Breast Cancer. F. Hernaman-Johnson.—p. 297.
Marble Bones: Case. J. S. Verco.—p. 311.
Dosage System for Interstitial Radium Therapy: Part II. Physical Aspects. H. M. Parker.—p. 313.

British Medical Journal, London

1: 989-1036 (May 7) 1938

Clinical Bearings of Parathyroids. W. J. E. Jessop.—p. 989.
*Laboratory and Clinical Investigations on Tuberculin Purified Protein Derivative (P. P. D.) and Old Tuberculin (O. T.). A. T. Doig, G. Gemmill, G. G. Kayne, F. V. Linggood, H. J. Parish and J. S. Westwater.—p. 992.
Causes of Hemorrhage from the Rectum. J. P. Lockhart-Mummery.—p. 997.
Observations on Dysenteric Conditions Among Europeans of Calcutta. B. P. Tribedi and M. N. De.—p. 1000.
*Prevention of Measles in a Children's Hospital. W. E. Crosbie.—p. 1003.

Investigations on Tuberculins.—Doig and his collaborators compare the potency and stability of the purified protein derivative of tuberculin and of "dried dilutions" of the derivative with that of old tuberculin in a series of laboratory and clinical investigations. The purified protein derivative is the most suitable reagent for the Mantoux test. It is almost invariably of constant potency on a weight basis, is stable in the dry state and is of a nonsensitizing nature. It is therefore particularly suitable for use in widespread surveys in which uniformity in the amount of the active principle injected is essential. Dried dilutions are likewise of stable and of uniform potency and can be prepared from purified protein derivative. The dried dilutions may be redissolved easily and quickly in a suitable borate buffer solution immediately before use. A series of "dried dilutions" of purified protein derivative has been compared with corresponding dilutions of international standard old tuberculin by means of the Mantoux test, titrated previously on sensitive guinea pigs. The preparations (on intracutaneous test) were almost equal in potency; only the most sensitive guinea pigs indicated that the "dried dilutions" were slightly stronger. The reactions obtained with purified protein derivative were similar in character to the response with old tuberculin both in guinea pigs and in human subjects. Clinical comparison, by measurement and the relative number of positive and negative reactions, indicated that the purified protein derivative was slightly more potent than the old tuberculin. The results suggest that if the Mantoux test were to be used as a method of comparing the potency of two tuberculins it would be necessary to have observations on a large number of patients before any conclusion could be drawn. There would appear to be no advantage in using human subjects instead of guinea pigs for the titration of old tuberculin. The deterioration of dilutions of old tuberculin in phenol saline is not sufficient to prevent their use for Mantoux tests if they have been kept up to six weeks at room temperature or nine weeks in the ice box. "Dried dilutions" of purified protein derivative are much more stable and have shown no detectable loss in potency after three years at room temperature.

Prevention of Measles.—The occurrence of measles in a children's ward can best be prevented by the system of nursing children in cubicles. In the absence of cubicles the only measures available are the passive immunization of contacts by serum from patients convalescing from measles, serum from adults who have had measles, immune globulin and whole blood. Crosbie avers that during the past winter a considerable number of cases of measles arose in the wards of Alder Hey and Olive Mount hospitals, with the result that it was necessary to immunize many contacts. The substances used for the purpose were serum from adults who have had measles and immune globulin from placental extract in varying doses. All susceptible contacts (289) were given an immunizing dose as soon as a case of measles was diagnosed in the ward. The best results were obtained from the use of 15 cc. of adult human serum or 10 cc. of immune globulin. Smaller doses of immune globulin did not give the same degree of protection, and of the forty-eight children receiving 4 cc. twelve did not obtain sufficient immunity to modify the course of the disease. However, no complications or sequelae occurred in these twelve children. Passive immunization against measles prolongs the period of incubation. One should wait for at least twenty-one days before admitting other susceptible children into the ward. A child may not be protected against measles even if he has been immunized from twelve to fourteen days previous to exposure to infection. The dosage of human serum or immune globulin should not be influenced by age. Children between 1 and 5 years of age require a full immunizing dose. In hospital practice droplet infection is not the sole means by which the infective material is carried from one patient to another; the nurses' hands may also be an important medium of conveyance.

Edinburgh Medical Journal

45: 309-372 (May) 1938

Medical Practice of the Future. J. Purves-Stewart.—p. 309.
Clinical Recollections and Reflections: XXIV. The Psychologic Problem of Venereal Disease. R. C. L. Batchelor.—p. 321.
The Lung and Pleura: Certain Anatomic Facts in Relation to Disease. A. F. Hewat.—p. 326.
*Nasal Sinusitis and Mental Disorder: Survey of 818 Cases. A. B. Smith and C. M. Ross.—p. 343.
Benign Intrathoracic Tumors: Notes on Two Cases. E. Bloch.—p. 357.
The Milk Supply. A. S. M. Macgregor.—p. 363.

Nasal Sinusitis and Mental Disorder.—Smith and Ross examined the nose, throat and ears of 818 mentally ill patients at the Royal Edinburgh Hospital. These patients were not selected; only those who were unable to be transferred to the examination room were omitted. Twenty-three showed no symptoms or signs of nasal sinus disease, but because of their mental or physical condition transillumination or x-ray examination was not carried out. Of the 795 remaining patients sixty-three, or 7.9 per cent, showed definite evidence of nasal sinusitis, 624 could be definitely regarded as being free from sinus disease, while in the remaining 108 patients, or 13.6 per cent, the presence of nasal sinus disease was indeterminate. These 108 patients showed opacity of one or more sinuses on transillumination. In all, ninety-three x-ray examinations were conducted, and of these sixty-five, or 69.9 per cent, revealed no sinus infection while twenty-eight, or 30.1 per cent, revealed definite sinusitis. It is thus probable that, had x-ray examination been carried out in the 108 indeterminate cases, thirty-two would have shown evidence of nasal sinusitis. On this assessment it may be estimated that of 795 patients with a mental disorder, ninety-five, or 11.9 per cent, had nasal sinusitis. Only one of sixteen patients with sinusitis operated on showed any improvement in the mental state. This improvement was of only a temporary nature. Since there is no evidence that infection of the nasal sinuses plays any fundamental part in the causation of the vast majority of cases of mental disorder, these patients should be spared the needless suffering attending surgical intervention.

Chinese Medical Journal, Peiping

53: 313-412 (April) 1938

Past and Present Trends in Medical History of China. L.-T. Wu.—p. 313.
Some of Dr. Hobson's Medical Works in the Chinese Language. C. S. Yang.—p. 323.
Men of Note in History of Leprosy of the East. L. S. Huizenga.—p. 335.
Dietary Principles in Ancient Chinese Medicine. H. C. Hou.—p. 347.
Chinese Materia Medica: Review of Some of the Work of the Last Decade. B. E. Read.—p. 353.
Posology of Chinese Drugs. F. P. Yueh; translated by K. L. Chang.—p. 363.
History of Chinese Spectacles. C. P. Rakusen.—p. 379.

Archives des Maladies du Cœur, Paris

31: 477-568 (May) 1938

*Respiratory Variations of Cardiac Systole and Arterial Pressure. E. Rist.—p. 477.
Parasystoles with Slow Rhythm and Mechanism of Rhythmic Extrasystoles. E. Doumer.—p. 491.
Electrocardiogram of Human Fetus. M. P. Marcel and J. P. Exchaquet.—p. 504.
Annular Peristaltic Systole. R. Lütembacher.—p. 513.
Auricular Tremulation and Bradycardia by Complete Auriculoventricular Dissociation. C. Lian and J.-J. Welti.—p. 518.
Electrocardiographic Changes Observed in Man Dead from Cold. W. Tomaszewski.—p. 525.

Respiratory Variations of Cardiac Systole.—Rist calls attention to kymographic studies on the respiratory variations of the cardiac pulsations during normal and pathologic conditions, which were carried out by Bascourret and Fischgold. These authors were able to register graphically what they term the increase of the pulsatility of the heart in expiration, a phenomenon which before could be estimated only by roentgenoscopy. Rist, after calling attention to some of his own earlier studies on this problem, points out that two distinct phenomena have often been confused—on the one hand, respiratory arrhythemia, which consists in an inspiratory acceleration of the cardiac rhythm, on the other hand the inspiratory weakening of the pulse, which is known as the paradoxic pulse of Kussmaul. The inspiratory weakening of the pulse, a phenomenon which is entirely different from its retardation, corresponds to an inspiratory reduction of the blood pressure. The author cites several examples of the confusion between the notion of retardation and that of weakening of the pulse. Some think that the arterial pressure decreases during inspiration and increases during expiration, while others maintain that quiet natural inspiration is generally accompanied by an elevation and the expiration by a reduction of the blood pressure; in artificial respiration exactly the opposite is the case. The thought that arterial pressure increases progressively from the beginning to the end of inspiration and decreases progressively from the beginning to the end of expiration is probably why Kussmaul saw in the inspiratory weakening of the pulse a paradoxic phenomenon. The author directs attention to the interminable conflict between two antagonistic factors: the action of the inspiratory muscles on the one hand and the elasticity of the lung on the other hand. The elastic traction of the lung increases with inspiration and diminishes with expiration. The result is that the amplitude of the heart beat diminishes with inspiration. This is not a question of diminution of the cardiac pulsatility, as has been stated, but it is rather the elastic resistance opposed to the cardiac contraction by the distended lungs, which grows with the inspiration. It results also in a lesser energy of the systole at the time of inspiration and consequently a diminution of the arterial pressure. But it is not obligatory and if the inspiratory distention of the elastic lung controls the systole it reduces also the energy of the traction from within outward which is exercised by the inspiratory musculature. The author shows further what happens if the lung is transformed into a nonelastic organ or when the contact between the heart and the lung is interrupted by the interposition of air, as is the case in pneumothorax. In this case the amplitude of the cardiac beat is considerably augmented and does not vary according to the phases of the respiratory activity. The author thinks that it will be highly instructive to register by means of the kymograph the various aspects of the action exerted on the heart by the respiratory function.

Presse Médicale, Paris

46: 865-880 (June 1) 1938

Instability of Vagosympathetic System and the Interventions on Sympathetic System in Course of Pulmonary Tuberculosis. L. Michon, J. Chaize and H. Mollard.—p. 865.
Existence of Aerophagy. G. Leven.—p. 868.
*Reflexotherapy of Neurotonic Reactions. L. Alquier.—p. 869.

Reflexotherapy of Neurotonic Reactions.—Alquier points out that the volume and the consistency of the flesh depends not only on the anatomic conditions (musculature, adipose tissues, blood, lymph and exudates) but also on the play of what Laubry terms "neurotonic reactions." The manual excitation of these reactions produces a true reflexotherapy. The author differentiates three types of neurotonic reactions: 1. The massage of the muscles, the stimulation of their insertions or of the para-articular tissues, which increases the muscular tonus and contractility. The arrest of the hypertonic conditions (excessive fatigue, cramps, contractures even with retractions, rigidity) is obtained by pinching the skin in a manner to provoke expansion of the interstitial tissues. 2. The vasomotoricity is nearly always locally regulable at will. Perpendicular pressure on the axis of an artery, stretching in the direction of the arterial current, augments the output and the pulsatility of the vessel. 3. The bringing into suitable tension by stretching or by manipulation with supple hands relaxes the rigidities. This relaxation affects not only the musculature but also the interstitial tissues. The author studied the retractility of the tissues for twenty years. He also thoroughly investigated the technic and results of reflexotherapy. He emphasizes that it is necessary to find the reflexogenic points which control the reactions. At these points the massage with rigid fingers or pressing maneuvers provoke an irritative spasmodic retraction; stretchings or a mild effleurage realizes a relaxation. The author further discusses the acute and chronic changes in retractility of the tissues and how they are counteracted by the reflexotherapy. He regards the relaxation of the hypertonic conditions of the muscles as the main objective of reflexotherapy. Congestion dominates the clinical picture at the onset of the acute infections. To counteract this congestion is the essential factor. However, a definite result can be obtained only by adjustment of the neurotonic retractility, suppressing the reflexogenic points and reestablishing the normal course of the lymph in the lacunar system and in the lymphatic drainage passages. The neurotonic retractility of the tissues varies according to the vagosympathetic excitability and the nature of the exudates. The technic of the reflexotherapy must be adapted to the neurohumoral conditions existing in the individual case. Soothing of the reflexogenic points and the clearing up of the lymphatic engorgements require the methodical application or reflexotherapy. The hands provoke the reactions and modify the excitation according to the response of the reflexes. The manual reflexotherapy is completed by various means: by deep kneading, by massage with beaters or chains and in some cases by mechanical vibrations. Further the author mentions thermophototherapy and various types of electrical treatments.

Monatsschrift für Psychiatrie und Neurologie, Basel

99: 1-560 (April) 1938. Partial Index

Epilepsy in Hydrocephalus. E. Fünfgeld.—p. 1.
Late Form of Amaurotic Idiocy with Aspects of Paralysis Agitans. J. Hallervorden.—p. 74.
Syndromes of Thalamus and Subthalamus and Disturbances of Thalamic Nuclei. K. Kleist and J. Gonzalo.—p. 87.
Status and Development of Knowledge About Intracranial Pressure. F. Sauerbruch.—p. 192.
Olfactory Disturbances and Horner's Syndrome After Traumas of the Head. E. Stier.—p. 201.
Early Diagnosis of Tumor of Auditory Nerve. K. Vogel.—p. 227.
*Demonstration of Tumor Cells in Cerebrospinal Fluid. H. G. Creutzfeldt and R. Riebler.—p. 488.

Tumor Cells in Cerebrospinal Fluid.—Of specimens of cerebrospinal fluid which had been obtained by lumbar puncture and which had been examined by Alzheimer's method, Creutzfeldt and Riebler selected those of nineteen cases in which the diagnosis had been based on the presence of tumor cells in the fluid and in which the correctness of the diagnosis had been established by biopsy or necropsy. In these cases they compared the results of Alzheimer's method of embedding and sectioning with those of Forster's simple drop or smear method. In the nineteen fluids obtained by lumbar puncture, Alzheimer's embedding method disclosed the presence of blastoma cells sixteen times, whereas Forster's drop or smear method revealed such cells only six times. The tests were made also on three specimens of fluid obtained by ventricular puncture and on five specimens obtained by the puncture of cysts in cases of tumor. In these specimens it was again possible to demonstrate the superiority of Alzheimer's method over the dry method.

Monatsschrift f. Geburtshülfe u. Gynäkologie, Basel

107: 257-380 (April) 1938. Partial Index

*Experiences with Hormone Pregnancy Reaction According to Aschheim-Zondek and Friedman-Lapham. A. Mekler.—p. 257.
Causes of Third Degree Tears of Perineum and Efforts to Prevent Them. L. Végh.—p. 296.
Experimental Examination of Etiology and Nature of Cystorectocele. R. Börner.—p. 304.
Rupture of Symphysis During Delivery. K. Kimmig.—p. 328.

Hormone Pregnancy Reactions. — Mekler's report is based on 1,360 hormone pregnancy reactions that were carried out at the women's clinic of the University of Zurich in the years 1930 to 1935 inclusive. In 676 cases the mouse test of Aschheim-Zondek was used and in 684 the rabbit test of Friedman-Lapham. It was found that the reliability of the mouse test was 96.6 per cent, that of the rabbit test 93.1 per cent. If the doubtful reactions are disregarded, the figures are 97.8 and 97.4 per cent, respectively. The reaction gives positive results a few days after the first missed menstruation and produces reliable results as early as eight days after the first menstrual omission. In cases of abortion and extra-uterine pregnancy, it was observed that the disappearance of the positive reaction is dependent on the clinical symptoms. The more severe the clinical symptoms of the abortion or the extra-uterine pregnancy, the sooner does the reaction become negative; however, the more subdued the clinical aspects, the longer does the positive reaction persist. The three degrees of the anterior pituitary hormone reaction as distinguished by Aschheim and Zondek are: reaction I, the presence of large, ripe follicles with extensive cavity formation; reaction II, the presence of blood-filled, ripe follicles, blood dots; and reaction III, the presence of corpora lutea, which enclose the ovum, corpora lutea atretica. Discussing the ovarian reaction I in the mouse method, Mekler says that Zondek and Aschheim demanded reaction II or III for a definite diagnosis of pregnancy, because they observed reaction I also in some cases in which pregnancy was absent. Mekler thinks that during the early period of pregnancy reaction I may be taken as an indication of pregnancy in a woman with normal genitalia and when tumor, severe endocrine disturbances and the preclimacteric can be ruled out. In extra-uterine pregnancy reaction I is of such frequent occurrence that together with the clinical aspects it is of considerable diagnostic value. Reaction I is to be regarded as an intermediate reaction in case of transition from negative to positive (early pregnancy) and from positive to negative (abortion, dead fetus, extra-uterine pregnancy). In the rabbit method, however, the rupture of the follicle does not have the significance of a transitional reaction, because in rabbits a spontaneous rupture of the follicle is possible. A comparison of the mouse test and of the rabbit test suggests that it is best to use both types of animals for the diagnosis of pregnancy: in the earliest stages of pregnancy and in the observation of the disappearing symptoms of pregnancy the mouse test is better, because reaction I can be utilized; however, for greater rapidity of the diagnosis of pregnancy the rabbit test is advisable.

Pediatria, Naples

46: 381-476 (May 1) 1938

Indications and Results of Tonsillectomy: Study Based on Observation of 418 Children After Adenotonsillectomy. F. Tecilazic.—p. 381.
*Encephalographic Aspects of Epilepsy in Children. R. Ruggeri.—p. 397.
Problems of Specific Treatment of Tuberculosis. L. Franzi.—p. 422.
Pigmented Urticaria in Girl with Chronic Erythroleukemic Myelosis of Cooley's Type. I. Gatto.—p. 429.
Tracheobronchial Adenopathy with Stenosis of Trachea and of Right Bronchus: Death from Asphyxia. C. Gabriele.—p. 452.

Encephalographic Aspects of Epilepsy.—Ruggeri made encephalograms of fifty-nine children and two adults with epilepsy. He found that the most frequent alteration shown by the encephalogram is the enlargement of the ventricles alone or combined with dilatation or lack of filling of the subarachnoid spaces. The encephalogram in hemiparesis showed bilateral asymmetric enlargement of the lateral ventricles, displacement of the ventricular system over the less affected side and alterations of the subarachnoidal spaces. In bilateral hypertonia with pyramidal symptoms and in epileptic dementia it showed great bilateral enlargement of the lateral ventricles and alterations or absence of the subarachnoidal spaces. The lateral and third ventricles were enlarged in epilepsy with changes of the character and in pyknolepsy. In a case of grave amblyopia the occipital poles of the lateral ventricles were greatly enlarged. In two cases of grave familial amblyopia in adults there was diffuse cortical atrophy. In the author's group, twenty patients were intellectually normal. The encephalogram was normal in eight. It showed alterations of the type of hemiparesis in four, diffuse cortical atrophy, especially in the parieto-occipital zone, in two, atrophy of the vertex in one and ventricular dilatation in five. There were seventeen cases of idiocy. In eleven of these cases there was great enlargement of the ventricles, in four of which there was also cortical atrophy. In one case of microcephalus and one of congenital syphilis the subarachnoidal spaces were insufficient and the right ventricle was deformed. The encephalogram was normal in two cases of tuberous sclerosis. It showed asymmetric enlargement of the lateral ventricles, one of which was greatly deformed. In an epileptic idiot the air failed to enter the ventricles and the subarachnoidal spaces. The author found no relation between the frequency and the intensity of the attacks and the aspect of the encephalogram. As a rule the encephalograms which show great changes are of patients with extreme mental derangement. The patients with encephalograms which show slight or no pathologic changes react well to the sedative treatment (barbital or bromide), especially if given without interruption, even with small doses. The author concludes that encephalography is of value in the etiologic diagnosis of epilepsy and as a guide for determining the type (sedative, medical or surgical) of the treatment.

Rivista di Patologia e Clin. d. Tubercolosi, Bologna

12: 289-368 (May 31) 1938

*Clinical and Statistical Study of Children Vaccinated with BCG and Maragliano Vaccines from 1932 to 1934 and of Nonvaccinated Children. Raffaella Faggioli.—p. 289.
Sedimentation Speed of Erythrocytes in Pulmonary Tuberculosis. O. Parenti.—p. 311.
Fibrothorax and Relative Insufficiency of Pulmonary Valve: Cases. Nicola Cavarozzi.—p. 336.
Pathogenesis of Pleurisy in Course of Artificial Pneumothorax. D. Giaquinto.—p. 343.

Vaccination for Tuberculosis. — Faggioli studied three groups of newborn infants: fifty-four were given the BCG vaccine, forty-six the Maragliano vaccine of killed tubercle bacilli and seventy-six were not vaccinated. The infants who received the BCG vaccine could not be isolated for the first six weeks following vaccination. Fifteen infants in the first group (those who received the BCG vaccine), ten in the second group (those who were given the Maragliano vaccine) and twenty-five in the third group (nonvaccinated infants) developed tuberculosis within the next three years. Four infants in the first group, three in the second and three in the third did not develop tuberculosis but were living in a contagious environment. Allergy developed within the fourth and ninth months of life in half of the tuberculous infants of the first and second groups, in four tuberculous infants who had not had any vaccine, in two of the four normal children in the BCG group who were living in a contagious environment, and in a normal infant who was also living in a contagious environment and had not been vaccinated. The effects of the vaccines on general and tuberculous mortality were verified in 395 infants also placed in three groups: 141 for the BCG, ninety-three for the Maragliano vaccine and 161 who did not receive any vaccines. Three infants in the BCG group and two in the control group died from tuberculosis. The author concludes that both the BCG and the Maragliano vaccines are harmless. Both vaccines diminished tuberculous morbidity and the rate of general morbidity. Tuberculous mortality does not take place in infants who had Maragliano vaccine. It is moderate in the group of nonvaccinated infants and greater in the BCG group if the children are not isolated after vaccination and the vaccine is administered only once. It is advisable to isolate the children in the preallergic phase, especially if they live in a contagious environment, to repeat the administration of BCG vaccine at the first,

third, seventh and fifteenth years of life and to make frequent examinations of children for an early diagnosis and an early hygienic and medical treatment.

Archivos Argentinos de Pediatría, Buenos Aires

9: 217-328 (March) 1938. Partial Index

*Acute Postinfectious Encephalitis in Children. A. Gareiso and P. O. Sagreras.—p. 217.
Humoral Chemistry: Diagnosis and Treatment of Congenital Stenosis of Pylorus. J. P. Garrahan and C. Ruiz.—p. 237.
Prognosis and Treatment of Congenital Myxedema. J. C. Pellerano.—p. 245.
Treatment of Gonorrhea in Children. J. J. Reboiras.—p. 252.
Huge Tuberculous Cavity in Infant: Case. M. Acuña and A. C. Gambirassi.—p. 265.

Acute Encephalitis After Infections.—Gareiso and Sagreras report forty-seven cases of acute encephalitis in infants and children. Fourteen of the cases were observed by the authors, and the others were from the Argentine literature. The disease develops with acute symptoms, the most frequent of which are convulsions, paralysis, sensorial disturbances and meningeal symptoms without changes of the cerebrospinal fluid. Acute encephalitis develops within two or three weeks in the course of whooping cough, in from four to six days in the course of measles, from one to three weeks in the course of diphtheria and either simultaneously with pneumonia, bronchopneumonia and influenza or in the course of these diseases. Acute encephalitis in whooping cough may develop with the common symptoms or with fever and mental torpor. Ataxia is frequently present. The disease is of long evolution with recurrences. The cerebral lesions are caused by the toxic and infectious effect of the virus. The rate of mortality is high. Acute encephalitis in measles may develop with the common symptoms or with coma and mental disorders. Ataxia is frequently present. Syphilitic neuropathic and alcoholic hereditary taints have an unfavorable effect on the evolution of the disease, which lasts from eight days to three months and leaves mental and motor sequels which are slowly controlled. The rate of mortality is low. Acute encephalitis in diphtheria is grave because of the nervous and cardiac disorders which it induces. Hemiplegia appears early and as a rule is permanent and complicated by athetosis or epilepsy. Acute encephalitis in pneumonia and bronchopneumonia is more frequent in infants than in older children. It may develop with the usual symptoms or with fever and mental disorders. Myocarditis and hemiplegia with contracture are the most common sequels. The disease lasts for a few days or for some months. The author calls special attention to encephalitis complicating influenza, two cases of which are reported. The patients suffered in early infancy from influenza complicated by acute suppurative otitis with mastoid edema in one case and by recurrent phlegmons of the hand and hip joint in the other. Epilepsy developed immediately in one patient and at the age of 5 in the other. The author states that the reflexes, in postinfluenzal encephalitis, may be normal or diminished in the absence of pyramidal symptoms or increased in the presence of symptoms. In the author's cases there were dystonia and hemiballism. The involuntary movements were of the choreic-athetosic type with tremors or hemiballism. The author concludes that encephalitis after influenza is uncommon. It carries a benign prognosis for life but the nervous sequels are permanent.

Frankfurter Zeitschrift für Pathologie, Munich

52: 1-162 (May 18) 1938. Partial Index

Gastric Carcinomas with Structure Resembling Chorionepithelioma. K. Gaertner.—p. 1.
Statistics on Carcinoma in Young Persons. G. Gutmann.—p. 15.
Primitive Leiomyomyxosarcoma of Prostate in Child with Diffuse Infiltration of Entire Wall of Bladder. S. Tovaru and C. Vasilescu.—p. 41.
Frequent ("Epidemic") Occurrence of Tumors in Group of One Hundred Chickens. E. Ask-Upmark.—p. 51.
Multiple Sclerosis of Endocrine Glands. F. Meerwein.—p. 54.
Fatty Infiltration of Organs in Case of Oxygen Deficiency and Starvation. H. Ulrich.—p. 80.
*Histologic Examination of Hypothalamus in Ordinary Obesity, in Morgagni's and Günther's Syndromes and in Morbus Cushing. W. Ritter.—p. 149.

Histologic Examination of Hypothalamus in Obesity.—Ritter made microscopic studies on the hypothalamus and the adjoining regions in four different types of obesity: so-called constitutional obesity, Morgagni's syndrome (endocraniosis hyperostotica with obesity and virilism), Günther's syndrome (cerebral polyglobulism) and Cushing's disease. The aim was to detect possible morphologic changes. Whereas the results of this examination were entirely negative, the hypophysis showed a severe basophilism in all four types of obesity. Moreover, examination of the adrenals disclosed a lipoid hyperplasia of the adrenal cortex. Various reasons, which the author discusses, seem to indicate that the basophilism of the hypophysis is not the cause of the obesity but rather represents a compensatory process elicited by the disturbance in the equilibrium of the endocrine organs involved in the fat metabolism. In this connection the author points out that the formation of adenomas in the parathyroids in a number of bone diseases (rickets, osteitis deformans, osteomalacia) is likewise regarded as a secondary process, an adjustment to the changed conditions in the calcium metabolism. The changes, which were found in the anterior lobe of the hypophysis in all four types of obesity, corroborate the relations between the basophil cells of the hypophysis and the fat metabolism, to which attention had been called by E. J. Kraus.

Klinische Wochenschrift, Berlin

17: 689-720 (May 14) 1938. Partial Index

Functions of Hypophysis. A. Jores.—p. 689.
Physiologic Experiments on Animals on Action of Hormones of Male Gonads. W. Schoeller and M. Gehrke.—p. 694.
*Does Physical Exertion Increase Predisposition to Poliomyelitis? Epidemiologic Observation. B. de Rudder and G. A. Petersen.—p. 699.
Influence of Irradiation with Ultraviolet Light on Antigen-Antibody Reaction of Skin (Cutaneous Test). G. Albus and F. Feldermann.—p. 702.
*What Influence Has Dextrose on Inoculation Malaria? W. de Pay.—p. 703.
Determination of Lipoid Phosphorus in Small Quantities of Blood. H. G. Krainick.—p. 706.

Physical Exertion and Poliomyelitis.—De Rudder and Petersen say that a connection between great physical exertion and the development of poliomyelitis (in times of epidemics) has been suggested repeatedly on the basis of occasional observations. Nevertheless, a real causal connection has heretofore been disputed. Observations in the course of a severe local epidemic of poliomyelitis in a boarding school for boys between the ages of 13 and 19, however, seem to prove such a connection. The increased predisposition to poliomyelitis following great physical exertion was demonstrated by the fact that the epidemic showed two waves of exacerbation, each of which appeared a few days after strenuous athletic contests. The author gives a detailed description of the etiologic details of the epidemic. To avoid misunderstandings, he emphasizes that there is of course not necessarily always an association between physical exertion and the development of the poliomyelitis, for in the described epidemic only some of the boys who were exposed to the same exertions developed poliomyelitis. The physical exertion is to be regarded merely as a factor increasing the predisposition to the poliomyelitis.

Influence of Dextrose on Inoculation Malaria.—De Pay describes a newly discovered action of dextrose in malariotherapy. At the author's clinic it was customary to give, as a prophylactic measure, to patients who were to undergo malariotherapy, but who had cardiac, vascular or severe hepatic and renal disorders, an intravenous injection of a 25 or 30 per cent solution of dextrose. It was observed that in the patients who had received the dextrose injections the malarial incubation period was much longer and autohemotherapy and other provocative measures were necessary to make the malariotherapy active. Moreover, in some patients, who already had had several malarial attacks and who were given injections of dextrose to support the heart action, the fever attacks ceased. In trying to find an explanation for this action of dextrose, the author discusses various possibilities. Among others, tests were made to determine whether dextrose acts only on the malarial fever or also on hyperthermias of different origins. These tests revealed that the action of dextrose on malaria cannot be regarded as nonspecific and symptomatic. Discussing the possible specific action of dextrose on malaria, the author cites the clinical histories of some of the forty cases of malario-

therapy in which attempts were made to arrest the attacks by dextrose. His theory of the mode of action of dextrose on malaria is that the concentrated dextrose solution changes the osmotic equilibrium in the blood, causes a shrinkage of some of the erythrocytes, and thus withdraws nutrient substances from the protozoa; the weakened protozoa are then acted on more effectively by the liver and spleen. Regarding the practical value of his investigations, he says that this action of dextrose on malaria is not to make the proved malarial remedies superfluous. However, he says that especially in weakened patients the use of dextrose is of great value because it makes possible a temporary arrest of the fever, prevents a further exacerbation of malarial anemia and further loss of hemoglobin and malarial pigmentation and thus makes it unnecessary to arrest the malariotherapy prematurely.

Münchener medizinische Wochenschrift, Munich

85: 777-816 (May 27) 1938. Partial Index

*Breaking of Prostate Ring. O. Franck.—p. 777.
Medical Aspects of Problem of Suicide. G. Säker.—p. 782.
Isolated Inflammation of Sublingual Gland by Plaud-Vincent's Infection. E. Bock.—p. 786.
*Poisoning with Tea from Arnica Flowers. H. Schoenemann.—p. 787.
Experiences on Treatment of Coli Infection of Urinary Passages by Means of Mandelic Acid. H. Kunstmann.—p. 790.

Breaking of Prostatic Ring.—Franck reviews the opinions about the genesis of hypertrophy of the prostate and suggests a new method of treatment, the breaking of the prostatic ring. After explaining how he arrived at this method of opening the prostatic ring, he cites some of the advantages of this method and explains the mechanism. The procedure is as follows: He first makes a suprapubic urinary fistula, because, no matter what the condition of the patient, this minor intervention is less trying and less dangerous than repeated attempts at catheterization. The suprapubic drainage effects within eight or ten days such an improvement in bladder, kidney and heart that then the breaking of the prostatic ring is possible. This intervention is made on all patients who have tolerated the suprapubic drainage; the latter is, to a certain extent, the touchstone for the practicability of a therapeutic intervention. Moreover, since the breaking of the prostatic ring is less serious and of shorter duration than the formation of the suprapubic fistula and since the patient's condition is better now than at the first intervention, neither age nor the condition of the heart or kidneys can be regarded as a contraindication to the operation. Discussing the technic, the author says that after a widening of the suprapubic fistula (so that the forefinger can be passed through) the anterior and the posterior poles of the ring of the prostate are pinched through. In each case the one blade of the crushing instrument is passed through the urethral slit, while the other blade grasps the pole of the prostatic ring together with its coverings. The pinch grooves are then separated by means of scissors. The author admits that the intervention is not always so simple; on the other hand, incomplete opening of the prostatic ring may occasionally be helpful in overcoming the stenotic effect of the prostate. It is explained and shown by illustrations that the sagittal cleft, referred to in prostatic surgery as the anterior and posterior commissures of the prostatic ring, are the sites best suited for the opening. The intervention, which requires only about two minutes, is completed with the introduction of a suprapubic catheter and the irrigation of the bladder. The catheter is left in place until the urine is free from blood. The author describes the histories of eight cases, in which he performed this intervention. In the concluding summary he says that this method can be used in mild and severe cases and that it will probably produce the same permanent results as enucleation.

Poisoning with Tea from Arnica Flowers.—Schoenemann reports a case in which a man aged 30 was hospitalized with the diagnosis meningitis. The patient complained of severe headaches and abdominal pains. Consciousness was intermittently impaired. There was an aromatic odor to the breath, but this was not like acetone. The patient was fretful and then became apathic. The respiration was abnormal; the skin was dry and cool, and warmth had to be applied artificially. As the symptoms gradually subsided and the patient's condition improved, he reported that on return from his work he had made himself some tea and taken it. Shortly after that he had had vomiting and an attack of diarrhea. Then he had lost consciousness. To the question as to what type of tea he had taken he was unable to give a definite answer, for to him teas seemed to be all the same. When the six types of tea found in his home were shown to him, he pointed out the arnica flowers as the type he had taken. Poisoning with this type of tea is rare, since this tea is now employed almost exclusively for external use (washing of hair and so on) but not internally. Reviewing the older literature on arnica, the author points out that the flower as well as the root of arnica was in wide medical use 150 years ago. He cites quotations from older works, which, while recognizing the helpful effects of arnica in various disorders, also warn against careless use, because it may result in undesirable reactions.

Geneeskundig Tijdschr. v. Nederl.-Indië, Batavia

78: 1025-1088 (May 3) 1938

Nasopharyngeal Tumors. D. Den Hoed.—p. 1026.
Endemic Scleroma in a Minahassa Village. H. A. P. C. Oomen and L. Kirschner.—p. 1032.
*Sulfanilamide in Treatment of Trachoma. B. Lian.—p. 1058.
Blood Groups Among Inhabitants of Nias. J. H. Maasland.—p. 1066.

Sulfanilamide in Trachoma.—Lian first describes two cases of trachoma that were refractory to all treatment and responded with temporary improvement to injections of a sulfanilamide preparation. Later another sulfanilamide preparation was given with good success by mouth. Favorable reports by another investigator on the effect of sulfanilamide in cases of trachoma induced the author to try the sulfanilamide medication on a larger material. He describes his observations on thirty patients with trachoma. In a table he indicates the doses given in each case and the effects obtained. With a few exceptions the cases were of the severe type, with corneal complications, which resulted in photophobia. The conjunctivitis and the corneal complications responded especially well to the sulfanilamide treatment, and the photophobia and the continuous lacrimation usually were greatly lessened. However, as regards the effect on the conjunctivitis and the corneal complications the action of sulfanilamide is not specific for trachoma, because other forms of conjunctivitis and corneal lesions have also been known to react favorably to sulfanilamide. The corneal complications of trachoma that were favorably influenced by the sulfanilamide were pannus, keratitis and ulcer. Moreover, after these complications had once been counteracted by the sulfanilamide preparation they rarely recurred. The sulfanilamide acted favorably also on the conjunctivitis and on the diffuse thickening of the conjunctiva. The author reaches the conclusion that, although sulfanilamide alone will not cure trachoma, it is a valuable aid in combination with the mechanical methods.

Hospitalstidende, Copenhagen

81: 393-420 (April 26) 1938

Focal Infection, Especially Stomatogenic: IX. Considerations on Causes and Nature of Diseases of Joints. E. Jarløv and O. Brinch.—p. 393.
*Id.: X. Concluding Considerations and Practical Results. E. Jarløv and O. Brinch.—p. 403.
After-Examination of "Psychopathic" Children. P. A. Schwalbe-Hansen.—p. 407.
True Diaphragmatic Hernia with Greater Part of Large Intestine as Content. K. Kalbak.—p. 416.

Focal Infections.—Jarløv and Brinch assert that a causal connection between focal infection and diseases of the joints is highly probable. Their experiments concern chronic disturbances of the joints. They believe that a considerable part of the large number of persons with polyarthritis can be helped by the disclosure of the infection foci and radical treatment in the early stages before the polyarthritis has caused irreparable injuries and before active secondary foci have formed in the lymph nodes and other tissues. They maintain with Pemberton and others that thorough examination and treatment along these lines should be a fixed part of diagnosis and treatment in polyarthritis. Important problems, they say, still await solution, particularly the question as to how the activity of the focus is to be determined. Intensive cooperation is called for on the part of internists, stomatologists, otologists, roentgenologists and bacteriologists and pathologists.